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(71) Applicants *(for all designated States except US)*: **GLAXOSMITHKLINE SPA** [IT/IT]; Via Alessandro Fleming, 2, I-37135 Verona (IT). **LABORATOIRE GLAXOSMITHKLINE S.A.S.** [FR/FR]; 100, route de Versailles, F-78163 Marly-le-Roi (FR).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **FARINA, Carlo** [IT/IT]; NiKem Research srl, Via Zambeletti, 25, I-20021 Baranzate di Bollate (IT). **GIARDINA, Giuseppe** [IT/IT]; NiKem Research srl, Via Zambeletti, 25, I-20021 Baranzate di Bollate (IT). **GRUGNI, Mario** [IT/IT]; NiKem Research srl, Via Zambeletti, 25, I-20021 Baranzate di Bollate (IT). **NADLER, Guy, Marguerite, Marie, Gerard** [FR/FR]; Laboratoire GlaxoSmithKline, 100, route de Versailles, F-78163 Marly-le-Roi (FR).

(74) Agent: **RUTTER, Keith**; Corporate Intellectual Property, SmithKline Beecham, 980 Great West Road, Brentford, Middlesex TW8 9GS (GB).

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(54) Title: NOVEL COMPOUNDS

(57) Abstract: Certain compounds of formula (I) or a pharmaceutically acceptable salts or hydrate thereof wherein R_1 is H or alkyl; R_2 is aryl or cycloalkyl or heteroaryl; R_3 is H or alkyl, optionally substituted by one or more fluorines; R_4 is $-NR_8R_9$ or R_{12}; r_8 is H or methyl; R_9 is H, alkyl, aryl, cycloalkyl or $R_{10}R_{11}$; or R_8 and R_9 together form a heterocyclic ring comprising 3-8 ringe members, which heterocyclic ring is optionally unsubstituted or is substituted one or more times by R_{11}; R_{10} is alkyl, aryl or cycloalkyl; R_{11} is carboxy or alkylcarboxy; R_{12} is R_{13} or OR_{13}; R_{13} is H or alkyl or aryl, optionally substituted by one or more fluorines; R_5 is branched or linear alkyl, cycloalkyl, cycloalkylalkyl, aryl, or a single or fused ring aromatic heterocyclic group; R_6 represents H or up to three substituents independently selected from the list consisting of: alkyl, alkenyl, aryl, alkoxy, hydroxy, halogen, nitro, cyano, carboxy, carboxamido, sulphonamido, alkoxycarbonyl, trifluoromethyl, acyloxy, amino or mono or di-alkylamino; R_7 is H or halo; a is 1-6; and any of R_2, R_5, R_9, and R_{10} may optionally be substituted one or more times by halo, hydroxy, amino, cyano, nitro, carboxy or oxo; a process for preparing such compounds, a pharmaceutical composition comprising such compounds and the use of such compounds and composition in medicine.

QUINOLINE-4-CARBOXAMIDE DERIVATIVES AS NK-3 AND NK-2 RECEPTOR ANTAGONISTS

The present invention relates to novel compounds, in particular to novel quinoline derivatives, to processes for the preparation of such compounds, to pharmaceutical compositions containing such compounds and to the use of such compounds in medicine.

The mammalian peptide Neurokinin B (NKB) belongs to the Tachykinin (TK) peptide family which also include Substance P (SP) and Neurokinin A (NKA). Pharmacological and molecular biological evidence has shown the existence of three subtypes of TK receptor (NK_1, NK_2 and NK_3) and NKB binds preferentially to the NK_3 receptor although it also recognises the other two receptors with lower affinity (Maggi et al, **1993**, *J. Auton. Pharmacol., 13*, 23-93).

Selective peptidic NK_3 receptor antagonists are known (Drapeau, **1990** *Regul. Pept.*, 31, 125-135), and findings with peptidic NK_3 receptor agonists suggest that NKB, by activating the NK_3 receptor, has a key role in the modulation of neural input in airways, skin, spinal cord and nigro-striatal pathways (Myers and Undem, 1993, *J.Physiol.*, 470, 665-679; Counture et al., 1993, *Regul. Peptides*, 46, 426-429; Mccarson and Krause, 1994, *J. Neurosci.*, 14 (2), 712-720; Arenas et al. 1991, *J.Neurosci.*, 11, 2332-8). However, the peptide-like nature of the known antagonists makes them likely to be too labile from a metabolic point of view to serve as practical therapeutic agents.

International Patent Application, Publication number WO 00/31037 discloses certain compounds stated to be non-peptide NK-3 antagonists and also to have NK-2 antagonist activity. These compounds are disclosed to be of potential use in the prevention and treatment of a wide variety of clinical conditions, which are characterised by overstimulation of the Tachykinin receptors, in particular NK-3 and NK-2.

We have now discovered a further novel class of potent non-peptide NK-3 antagonists. The new compounds are also far more stable from a metabolic point of

view than the known peptidic NK-3 receptor antagonists and are of potential therapeutic utility. The new compounds also have good NK-2 antagonist activity and are therefore considered to be of potential use in the prevention and treatment of a wide variety of clinical conditions which are characterised by overstimulation of the Tachykinin receptors, in particular NK-3 and NK-2.

These conditions include respiratory diseases, such as chronic obstructive pulmonary disease (COPD), asthma, airway hyper-reactivity, cough; inflammatory diseases such as inflammatory bowel disease, psoriasis, fibrositis, osteoarthritis, rheumatoid arthritis and inflammatory pain; neurogenic inflammation or peripheral neuropathy, allergies such as eczema and rhinitis; ophthalmic diseases such as ocular inflammation, conjunctivitis, vernal conjuctivitis and the like; cutaneous diseases, skin disorders and itch, such as cutaneous wheal and flare, contact dermatitis, atopic dermatitis, urticaria and other eczematoid dermatitis; adverse immunological reactions such as rejection of transplanted tissues and disorders related to immune enhancement or suppression such as systhemic lupus erythematosis; gastrointestinal (GI) disorders and diseases of the GI tract such as disorders associated with the neuronal control of viscera such as ulcerative colitis, Crohn's disease, irritable bowel syndrome (IBS), gastro-exophageous reflex disease (GERD); urinary incontinence and disorders of the bladder function; renal disorders; increased blood pressure, proteinuria, coagulopathy and peripheral and cerebral oedema following pre-eclampsia in pregnancies (hereinafter referred to as the 'Primary Conditions').

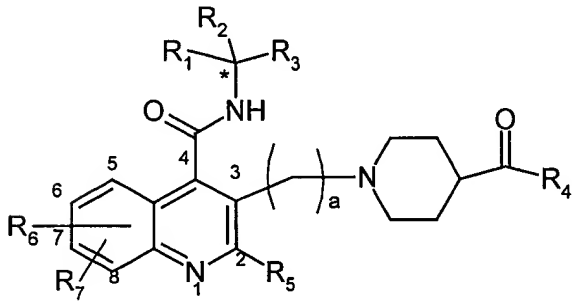
Certain of these compounds also show CNS activity and hence are considered to be of particular use in the treatment of disorders of the central nervous system such as anxiety, depression, psychosis and schizophrenia; neurodegenerative disorders such as AIDS related dementia, senile dementia of the Alzheimer type, Alzheimer's disease, Down's syndrome, Huntingdon's disease, Parkinson's disease, movement disorders and convulsive disorders (for example epilepsy); demyelinating diseases such as multiple sclerosis and amyotrophic lateral sclerosis and other neuropathological disorders such as diabetic neuropathy, AIDS related neuropathy, chemotherapy-induced neuropathy and neuralgia; addiction disorders such as alcoholism; stress related somatic disorders;

reflex sympathetic dystrophy such as shoulder/hand syndrome; dysthymic disorders; eating disorders (such as food intake disease); fibrosing and collagen diseases such as scleroderma and eosinophilic fascioliasis; disorders of the blood flow caused by vasodilatation and vasospastic diseases such as angina, migraine and Reynaud's disease and pain or nociception, for example, that is attributable to or associated with any of the foregoing conditions especially the transmission of pain in migraine, (hereinafter referred to as the 'Secondary Conditions').

The new compounds also show improved oral bioavailability.

The compounds of formula (I) are also considered to be useful as diagnostic tools for assessing the degree to which neurokinin-3 and neurokinin-2 receptor activity (normal, overactivity or underactivity) is implicated in a patient's symptoms.

According to the present invention, there is provided a compound of formula (I) below or a pharmaceutically acceptable salt or hydrate thereof:



(I)

wherein:

R_1 is H or alkyl;

R_2 is aryl or cycloalkyl or heteroaryl;

R_3 is H or alkyl, optionally substituted by one or more fluorines;

R_4 is $-NR_8R_9$ or R_{12};

R_8 is H or methyl;

R_9 is H, alkyl, aryl, cycloalkyl or $R_{10}R_{11}$; or R_8 and R_9 together form a heterocyclic ring comprising 3-8 ring members, which heterocyclic ring is optionally unsubstituted or is substituted one or more times by R_{11};

R_{10} is alkyl, aryl or cycloalkyl;

R_{11} is carboxy or alkylcarboxy;

R_{12} is R_{13} or OR_{13};

R_{13} is H or alkyl or aryl, optionally substituted by one or more fluorines;

R_5 is branched or linear alkyl, cycloalkyl, cycloalkylalkyl, aryl, or a single or fused ring aromatic heterocyclic group;

R_6 represents H or up to three substituents independently selected from the list consisting of: alkyl, alkenyl, aryl, alkoxy, hydroxy, halogen, nitro, cyano, carboxy, carboxamido, sulphonamido, alkoxycarbonyl, trifluoromethyl, acyloxy, amino or mono- or di-alkylamino;

R_7 is H or halo;

a is 1-6; and

any of R_2, R_5, R_9, and R_{10} may optionally be substituted one or more times by halo, hydroxy, amino, cyano, nitro, carboxy or oxo;

not being a compound wherein R_1 is H, R_2 is cycloalkyl, R_3 is methyl, R_4 is NH_2, R_5 is phenyl, and R_6 and R_7 are H.

Preferably, R_3 represents methyl or ethyl or isopropyl.

Suitably, R_2 represents unsubstituted phenyl or unsubstituted cyclohexyl.

Advantageously, R_1 is hydrogen.

In preferred embodiments, R_5 is unsubstituted phenyl.

Advantageously, each of R_6 and R_7 represents hydrogen.

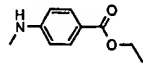
Suitably, a is 1, 2 or 3. Preferably, a is 1.

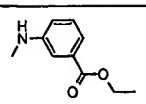
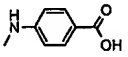
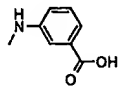
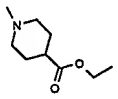
In some preferred embodiments, R_4 is $-NR_8R_9$ and R_8 and R_9 together with the N atom to which they are attached form a five- or six-membered saturated heterocyclic ring. Advantageously, said heterocyclic ring is substituted at least once by R_{11}. Said heterocyclic ring may for example be a six-membered ring which ring is substituted once at the meta- or para- position thereof by R_{11}.

In other advantageous embodiments, R_4 is $-NR_8R_9$ and R_8 is H and R_9 is H, alkyl, aryl, cycloalkyl or $R_{10}R_{11}$ where R_{10} is phenyl. Suitably, R_9 is $-R_{10}R_{11}$ and R_{11} is meta- or para- linked to said phenyl group R_{10}. Said R_{11} may be carboxylate or carboxyalkyl, such as carboxymethyl or carboxyethyl.

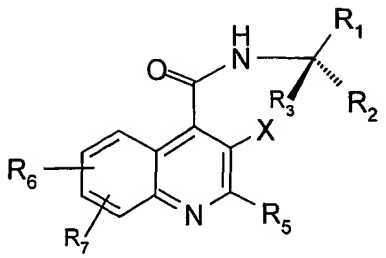
In yet other advantageous embodiments, R_4 is R_{12} and R_{12} is OH or OMe.

In especially preferred embodiments, a is 1, R_6 is H, R_1 is H, R_5 is unsubstituted phenyl, R_7 is hydrogen, and R_2, R_3 and R_4 are selected from the following combinations:

R_2	R_3	R_4
Phenyl	methyl	
Cyclohexyl	methyl	

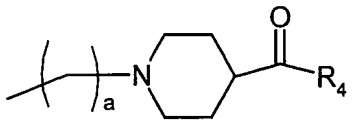
Cyclohexyl	methyl	
Cyclohexyl	methyl	
Cyclohexyl	methyl	
Cyclohexyl	methyl	
Cyclohexyl	methyl	
Cyclohexyl	methyl	
Cyclohexyl	methyl	
Cyclohexyl	methyl	-OH
Cyclohexyl	methyl	-OMe

The compounds of formula (I) may have at least one asymmetric centre - for example the carbon atom labelled with an asterisk (*) in the compound of formula (I) - and therefore may exist in more than one stereoisomeric form. The invention extends to all such stereoisomeric forms and to mixtures thereof, including racemates. In particular, the invention includes compounds wherein the asterisked carbon atom in formula (I) has the stereochemistry shown in formula (Ia):



(Ia)

wherein R_1, R_2, R_3, R_5, R_6, and R_7 are as defined in relation to formula (I), and X represents the moiety



The compounds of formula (I) or their salts or solvates are preferably in pharmaceutically acceptable or substantially pure form. By pharmaceutically acceptable form is meant, inter alia, having a pharmaceutically acceptable level of purity excluding normal pharmaceutical additives such as diluents and carriers, and including no material considered toxic at normal dosage levels.

A substantially pure form will generally contain at least 50% (excluding normal pharmaceutical additives), preferably 75%, more preferably 90% and still more preferably 95% of the compound of formula (I) or its salt or solvate.

One preferred pharmaceutically acceptable form is the crystalline form, including such form in pharmaceutical composition. In the case of salts and solvates the additional ionic and solvent moieties must also be non-toxic.

Suitable salts are pharmaceutically acceptable salts.

Suitable pharmaceutically acceptable salts include the acid addition salts with the conventional pharmaceutical acids, for example maleic, hydrochloric, hydrobromic,

phosphoric, acetic, fumaric, salicylic, citric, lactic, mandelic, tartaric, succinic, benzoic, ascorbic and methanesulphonic.

Suitable pharmaceutically acceptable salts include salts of acidic moieties of the compounds of formula (I) when they are present, for example salts of carboxy groups or phenolic hydroxy groups.

Suitable salts of acidic moieties include metal salts, such as for example aluminium, alkali metal salts such as lithium, sodium or potassium, alkaline earth metal salts such as calcium or magnesium and ammonium or substituted ammonium salts, for example those with lower alkylamines such as triethylamine, hydroxy alkylamines such as 2-hydroxyethylamine, bis-(2-hydroxyethyl)-amine or tri-(2-hydroxyethyl)-amine, cycloalkylamines such as bicyclohexylamine, or with procaine, dibenzylpiperidine, N-benzyl-β-phenethylamine, dehydroabietylamine, N,N'-bisdehydroabietylamine, glucamine, N-methylglucamine or bases of the pyridine type such as pyridine, collidine, quinine or quinoline.

Suitable solvates are pharmaceutically acceptable solvates.

Suitable pharmaceutically acceptable solvates include hydrates.

The term 'alkyl' (unless specified to the contrary) when used alone or when forming part of other groups (such as the 'alkoxy' group) denotes straight- or branched-chain alkyl groups containing 1 to 12, preferably 1-6 carbon atoms, examples include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl or tert-butyl group.

The term 'cycloalkyl' (unless specified to the contrary) when used alone or when forming part of other groups (such as the 'cycloalkylalkyl' group) denotes cyclic saturated or unsaturated carbon rings including 3-12, preferably 3-8 carbon ring members. Examples include cyclopropyl, cyclobutyl, cyclohexyl, cyclooctyl.

The term 'alkenyl' (unless specified to the contrary) when used alone or when forming part of other groups denotes straight- or branched- unsaturated carbon chains including at least one double C=C bond and containing 2-12, preferably 2-6 carbon atoms.

The term 'carbocyclic' denotes cycloalkyl and aryl rings.

The term 'aryl' denotes aromatic groups including phenyl and naphthyl, preferably phenyl which unless specified to the contrary optionally comprise up to five, preferably up to three substituents selected from halogen, alkyl, phenyl, alkoxy, haloalkyl, hydroxyalkyl, hydroxy, amino, nitro, cyano, carboxy, alkoxycarbonyl, alkoxycarbonylalkyl, alkylcarbonyloxy, or alkylcarbonyl groups.

The term 'aromatic heterocyclic group' denotes groups comprising aromatic heterocyclic rings containing from 5 to 12 ring atoms, suitably 5 or 6, and comprising up to four hetero-atoms in the or each ring selected from S, O or N.

Composite terms such as 'alkylcarboxy', 'cycloalkylalkyl' and so forth refer to components of a compound which include two inter-linked groups, with the group named latterly in the term being the linking group, so that 'alkylcarboxy' means (alkyl)-COO- whilst 'cycloalkylalkyl' means (cycloalkyl)-(alkyl)-.

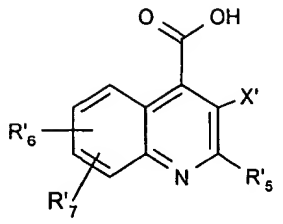
Unless specified to the contrary, suitable substituents for any heterocyclic group includes up to 4 substituents selected from the group consisting of: alkyl, alkoxy, aryl and halogen or any two substituents on adjacent carbon atoms, together with the carbon atoms to which they are attached, may form an aryl group, preferably a benzene ring, and wherein the carbon atoms of the aryl group represented by the said two substituents may themselves be substituted or unsubstituted.

It will be understood that unless otherwise specified, groups and substituents referred to herein are unsubstituted.

When used herein the term "halogen" or "halo" refers to fluorine, chlorine, bromine and iodine, preferably fluorine, chlorine or bromine.

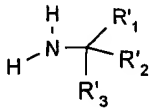
When used herein the term "acyl" includes residues of acids, in particular a residue of a carboxylic acid such as an alkyl- or aryl- carbonyl group.

The invention also provides in one aspect a process for the preparation of a compound of formula (I), or a salt thereof and/or a solvate thereof, which process comprises reacting a compound of formula (II) or an active derivative thereof:



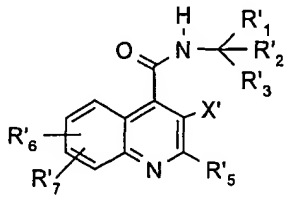
(II)

wherein R'_6, R'_7, R'_5 and X' are R_6, R_7, R_5 and X respectively as hereinbefore defined in relation to formula (I) or (Ia), or a group convertible to R_6, R_7, R_5 and X respectively; with a compound of formula (III):



(III)

wherein R'_1, R'_2, and R'_3 are R_1, R_2, and R_3 as defined for formula (I) or a group or atom convertible to R_1, R_2, and R_3 respectively; to form a compound of formula (Ib):



(Ib)

wherein R'_1, R'_2, R'_3, X', R'_5, R'_6 and R'_7 are as defined above, and thereafter carrying out one or more of the following optional steps:

(i) converting any one of R'_1, R'_2, R'_3, X', R'_5, R'_6 and R'_7 to R_1, R_2, R_3, X, R_5, R_6 and R_7 respectively as required, to obtain a compound of formula (I);

(ii) converting a compound of formula (I) into another compound of formula (I); and

(iii) preparing a salt of the compound of formula (I) and/or a solvate thereof.

Suitable groups convertible into other groups include protected forms of said groups.

Suitably R'_1, R'_2, R'_3, X', R'_5, R'_6 and R'_7 each represents R_1, R_2, R_3, X, R_5, R_6 and R_7 respectively or a protected form thereof.

It is favoured if the compound of formula (II) is present as an active derivative.

A suitable active derivative of a compound of formula (II) is a transient activated form of the compound of formula (II) or a derivative wherein the carboxy group of the compound of formula (II) has been replaced by a different group or atom, for example by an acyl halide, preferably a chloride, or an acylazide or a carboxylic acid anhydride.

Other suitable active derivatives include: a mixed anhydride formed between the carboxyl moiety of the compound of formula (II) and an alkyl chloroformate; an activated ester, such as a cyanomethyl ester, thiophenyl ester, p-nitrophenyl ester, p-nitrothiophenyl ester, 2,4,6-trichlorophenyl ester, pentachlorophenyl ester, pentafluorophenyl ester, N-hydroxy-phtalimido ester, N-hydroxypiperidine ester, N-hydroxysuccinimide ester, N-hydroxy benzotriazole ester; alternatively, the carboxy group of the compound of formula (II) may be activated using a carbodiimide or N,N'-carbonyldiimidazole.

The reaction between the compound of formula (II) or the active derivative thereof and the compound of formula (III) is carried out under the appropriate conventional conditions for the particular compounds chosen. Generally, when the compound of formula (II) is present as an active derivative the reaction is carried out using the same solvent and conditions as used to prepare the active derivative, preferably the active derivative is prepared *in situ* prior to forming the compound of formula (Ib) and thereafter the compound of formula (I) or a salt thereof and/or a solvate thereof is prepared.

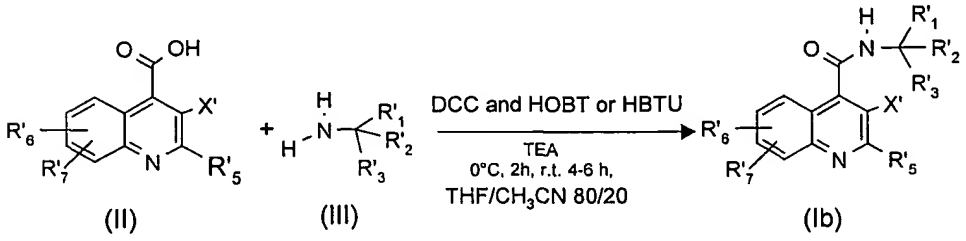
For example, the reaction between an active derivative of the compound of formula (II) and the compound of formula (III) may be carried out:

(a) by first preparing an acid chloride and then coupling said chloride with the compound of formula (III) in the presence of an inorganic or organic base in a suitable aprotic solvent such as dimethylformamide (DMF) at a temperature in a range from -70 to 50°C (preferably in a range from -10 to 20°C); or

(b) by treating the compound of formula (II) with a compound of formula (III) in the presence of a suitable condensing agent, such as for example N,N'-carbonyl diimidazole (CDI) or a carbodiimide such as dicyclohexylcarbodiimide (DCC) or N-dimethylaminopropyl-N'-ethylcarbodiimide, preferably in the presence of N-hydroxybenzotriazole (HOBT) to maximise yields and avoid racemization processes (see *Synthesis,* 453, 1972), or O-benzotriazol-1-yl-N,N,N',N'-tetramethyluroniumhexafluorophosphate (HBTU), in an aprotic solvent, such as a mixture of acetonitrile (MeCN) and tetrahydrofuran (THF), for example a mixture in a volume ratio of from 1:9 to 7:3 (MeCN:THF), at any temperature providing a suitable rate of formation of the required product, such as a temperature in the range of from -70 to 50°C, preferably in a range of from -10 to 25°C, for example at 0°C.

A preferred reaction is set out in Scheme 1 shown below:

Scheme 1



(II) (III) (Ib)

wherein R'_1, R'_2, R'_3, X', R'_5, R'_6 and R'_7 are as defined above.

In the case in which the corresponding alkyl (such as methyl or ethyl) ester of compound (II) is utilised, an hydrolysis to compound (II) is required before conversion

to compound (Ib) in Scheme 1. Such hydrolysis can be carried out under acidic conditions, such 10-36% hydrochloric acid at a temperature in the range between 30 and 100 °C.

It will be appreciated that a compound of formula (Ib) may be converted to a compound of formula (I), or one compound of formula (I) may be converted to another compound of formula (I) by interconversion of suitable substituents. Thus, certain compounds of formula (I) and (Ib) are useful intermediates in forming other compounds of the present invention.

Accordingly, in a further aspect the invention provides a process for preparing a compound of formula (I), or a salt thereof and/or a solvate thereof, which process comprises converting a compound of the above defined formula (Ib) wherein at least one of R'_1, R'_2, R'_3, X', R'_5, R'_6 and R'_7 is not R_1, R_2, R_3, X, R_5, R_6 or R_7 respectively, thereby to provide a compound of formula (I); and thereafter, as required, carrying out one or more of the following optional steps:

(i) converting a compound of formula (I) into another compound of formula (I); and

(ii) preparing a salt of the compound of formula (I) and/or a solvate thereof.

Suitably, in the compound of formula (Ib) the variables R'_1, R'_2, R'_3, X', R'_5, R'_6 and R'_7 are R_1, R_2, R_3, X, R_5, R_6 and R_7 respectively or they are protected forms thereof.

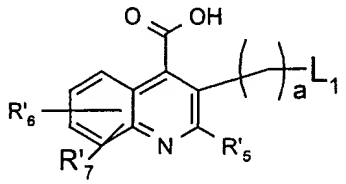
The above mentioned conversions, protections and deprotections are carried out using the appropriate conventional reagents and conditions and are further discussed below.

A chiral compound of formula (III) wherein R_2 is a C_5 or C_7 cycloalkyl group, R_3 is methyl and R_1 is H are described in J. Org. Chem. (1996), 61 (12), 4130-4135. A chiral compound of formula (III) wherein R_2 is phenyl, R_3 is isopropyl and R_1 is H is a known compound described in for example Tetrahedron Lett. (1994), 35(22), 3745-6.

The compounds of formula (III) are known commercially available compounds or they can be prepared from known compounds by known methods, or methods

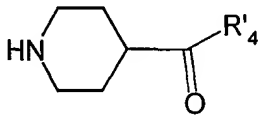
analogous to those used to prepare known compounds, for example the methods described in Liebigs Ann. der Chemie, (1936), 523, 199.

In some embodiments of the invention, a compound of formula (II) or the corresponding alkyl (such as methyl or ethyl) ester is prepared by reacting a compound of formula (IV) or the corresponding alkyl (such as methyl or ethyl) ester:



(IV)

wherein R'_6, R'_7, R'_5 and a are as defined above and L_1 represents a halogen atom such as a bromine atom, with a compound of formula (V):



(V)

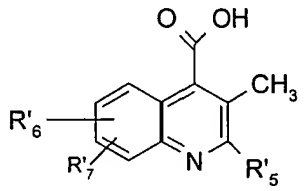
wherein R'_4 is R_4 as defined in relation to formula (I) or a protected form thereof.

Suitably, R'_4 is R_4.

Suitably, reaction between the compounds of formulae (IV) or the corresponding alkyl (such as methyl or ethyl) ester and (V) is carried out under conventional amination conditions, for example when L_1 is a bromine atom then the reaction is conveniently carried out in an aprotic solvent, such as tetrahydrofuran or dimethylformamide at any temperature providing a suitable rate of formation of the required product, usually at ambient temperature; preferably the reaction is carried out in the presence of triethylamine (TEA) or K_2CO_3.

The compounds of formula (V) are known, commercially available compounds or they can be prepared using methods analogous to those used to prepare known compounds; for example the methods described in the Chemistry of the Amino Group, Patais (Ed.), Interscience, New York 1968; Advanced Organic Chemistry, March J, John Wiley & Sons, New York, 1992 ; J. Heterocyclic Chem. (1990), 27, 1559; Synthesis (1975), 135, Bioorg. Med. Chem. Lett. (1997), 7, 555, or Protective Groups in Organic Synthesis (second edition), Wiley Interscience, (1991) or other methods mentioned herein.

In cases where a is 1, a compound of formula (IV) or the corresponding alkyl (such as methyl or ethyl) ester may be prepared by appropriate halogenation of a compound of formula (VI) or the corresponding alkyl (such as methyl or ethyl) ester:



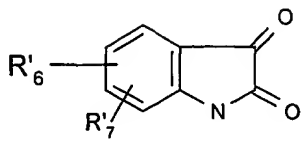
(VI)

wherein R'_6, R'_7 and R'_5 are as defined above in relation to formula (II).

Suitable halogenation reagents are conventional reagents depending upon the nature of the halogen atom required, for example when L_1 is bromine a preferred halogenation reagent is N-bromosuccinimide (NBS).

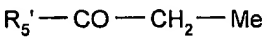
The halogenation of the compound of formula (VI) or the corresponding alkyl (such as methyl or ethyl) ester is suitably carried out under conventional conditions, for example bromination is carried out by treatment with NBS in an inert solvent, such as carbon tetrachloride CCl_4, or 1,2-dichloroethane or CH_3CN, at any temperature providing a suitable rate of formation of the required product, suitably at an elevated temperature such as a temperature in the range of 60°C to 100°C, for example 80°C; preferably the reaction is carried out in the presence of a catalytic amount of benzoyl peroxide.

A compound of formula (VI) is conveniently prepared by reacting a compound of formula (VII):



(VII)

wherein R'_6 and R'_7 are as defined in relation to formula (II), with a compound of formula (XIII):



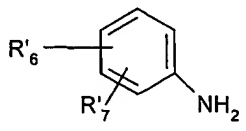
(XIII)

wherein R'_5 is as defined in relation to formula (II).

The reaction between the compounds of formula (VII) and (XIII) is conveniently carried out using Pfitzinger reaction conditions (see for example J. Prakt. Chem. 33, 100 (1886), J. Prakt. Chem. 38, 582 (1888), J. Chem. Soc. 106 (1948) and Chem. Rev. 35, 152 (1944)), for example in an alkanolic solvent such as ethanol, at any temperature providing a suitable rate of formation of the required product, but generally at an elevated temperature, such as the reflux temperature of the solvent, and preferably in the presence of a base such as potassium hydroxide or potassium tert-butoxide.

The compounds of formula (VII) are known compounds or they are prepared according to methods used to prepare known compounds for example those disclosed in J. Org. Chem. 21, 171 (1955); J. Org. Chem. 21, 169 (1955).

Alternatively a compound of formula (VI) may be conveniently prepared by reacting a compound of formula (XIV)



(XIV)

wherein R'_6 and R'_7 are as defined in relation to formula (II), with a compound of formula (XV):

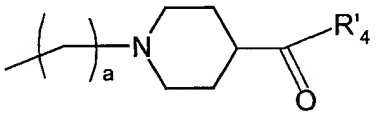
$$R_5'—CHO \qquad (XV)$$

wherein R'_5 is as defined in relation to formula (II) in presence of oxobutyric acid.

The reaction between the compounds of formula (XIV) and (XV) is conveniently carried out using Doebner reaction conditions (see for example Chem. Ber. 29, 352 (1894); Chem. Revs. 35, 153, (1944); J. Chem. Soc. B, 1969, 805), for example in an alcoholic solvent such as ethanol, at any temperature providing a suitable rate of formation of the required product, but generally at an elevated temperature, such as the reflux temperature of the solvent.

The compounds of formula (XIV) and (XV) are known compounds or they are prepared according to methods used to prepare known compounds for example as described in *Vogel's Textbook of Practical Organic Chemistry.*

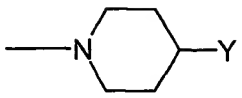
In some alternative embodiments of the invention, a compound of formula (II) wherein X' represents



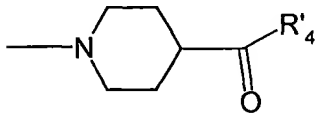
is prepared by reacting a compound of formula (VII) as defined above with a compound of formula (VIII):

$$R_5'—CO—CH_2—(CH_2)a—T_5 \qquad (VIII)$$

wherein R'_5 is as defined in relation to formula (II), and T_5 is a group

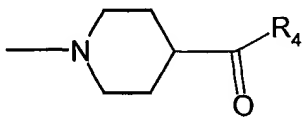


where Y is a group R'_4 as defined in relation to formula (I) or a protected form thereof or a group convertible thereto, and a is as defined in relation to formula (II); and thereafter as required removing any protecting group, for example by dehydrogenation, and/or converting any group T_5 to



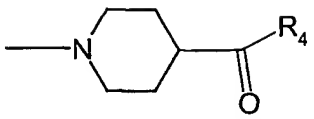
The reaction between the compounds of formula (VII) and (VIII) is conveniently carried out using Pfitzinger reaction conditions (see for example J. Prakt. Chem. 33, 100 (1886), J. Prakt. Chem. 38, 582 (1888), J. Chem. Soc. 106 (1948) and Chem. Rev. 35, 152 (1944)), for example in an alkanolic solvent such as ethanol, at any temperature providing a suitable rate of formation of the required product, but generally at an elevated temperature, such as the reflux temperature of the solvent, and preferably in the presence of a base such as potassium hydroxide or potassium tert-butoxide.

Protected forms of

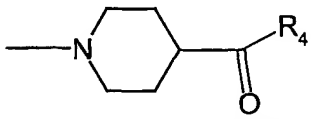


will vary according to the particular nature of the group being protected but will be chosen in accordance with normal chemical practice.

Groups convertible to

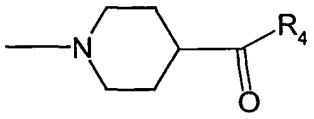


include groups dictated by conventional chemical practice to be required and to be appropriate, depending upon the specific nature of the

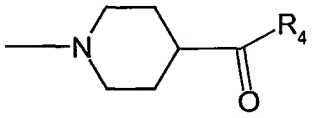


under consideration.

Suitable deprotection methods for deprotecting protected forms of



and conversion methods for converting T_5 to



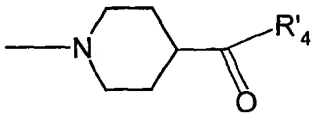
will be those used conventionally in the art depending upon the particular groups under consideration with reference to standard texts such as Greene, T.W. and Wuts, P.G.M. Protective Groups in Organic Synthesis, John Wiley & Sons Inc. New York, 1991 (Second Edt.) or in Kocienski, P.J. Protecting groups. George Thieme Verlag, New York, 1994 and Chemistry of the Amino Group, Patais (Ed.), Interscience, New York 1968; or Advanced Organic Chemistry, March J, John Wiley & Sons, New York, 1992.

A compound of formula (VIII) is prepared from a compound of formula (IX):

$$R_5' — CO — CH_2 — (CH_2)_a — OH \qquad (IX)$$

wherein R'_5 is as defined in relation to formula (II) and a is as defined in relation to formula (VIII), by first halogenating, preferably brominating, or mesylating the compound of formula (IX) and thereafter reacting the halogenation or mesylation product so formed with a compound capable of forming a group T_5 so as to provide the required compound of formula (VII).

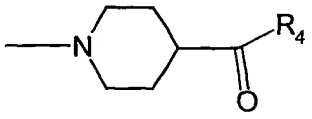
When T_5 is a group



a compound capable of forming a group T_5 is a compound of the above defined formula (V).

The halogenation of the compound of formula (IX) is suitably carried out using a conventional halogenation reagent. Mesylation is conveniently carried out using mesyl chloride in an inert solvent such as methylene dichloride, at a temperature below room temperature, such as 0°C, preferably in the presence of triethylamine.

The reaction conditions between the compound of formula (IX) and the compound capable of forming a group T_5 will be those conventional conditions dictated by the specific nature of the reactants, for example when the T_5 required is a group

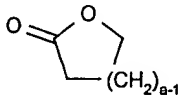


and the required compound capable of forming a group T_5 is a compound of the above defined formula (V), then the reaction between the halogenation or mesylation product of the compound of formula (IX) and the compound of formula (V) is carried out under

analogous conditions to those described for the reaction between the compounds of formulae (IV) and (V).

Other compounds capable of forming a group T_5 will depend upon the particular nature of T_5, but will be those appropriate compounds dictated by conventional chemical practice with reference to standard texts such as Chemistry of the Amino Group, Patais (Ed.), Interscience, New York 1968; and Advanced Organic Chemistry, March J, John Wiley & Sons, New York, 1992.

A compound of formula (IX) may be prepared by reacting a compound of formula (X):



(X)

wherein a is as defined in relation to formula (VIII), with a lithium salt of formula (XI):

$$R'_5\ Li \qquad (XI)$$

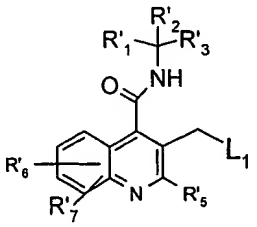
wherein R'_5 is as defined in relation to formula (II).

The reaction between the compounds of formulae (X) and (XI) can be carried out in an aprotic solvent, such as diethyl-ether at any temperature providing a suitable rate of formation of the required product, usually at a low temperature such as in the range of -10°C to -30°C, for example -20°C.

The compounds of formula (VII) are known compounds or they are prepared according to methods used to prepare known compounds for example those disclosed in J. Org. Chem. 21, 171 (1955); J. Org. Chem. 21, 169 (1955).

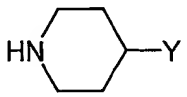
The compounds of formula (X) and (XI) are known compounds or they are prepared according to methods used to prepare known compounds for example those disclosed by Krow G. R. in Organic Reactions, Vol 43, page 251, John Wiley & Sons Inc.1994 (for the compounds of formula (X)) and Organometallics in Synthesis, Schlosser M.(Ed), John Wiley & Sons Inc.1994 (for the compounds of formula (XI)).

In another aspect, the present invention provides a process for the preparation of a compound of formula (I), or a salt thereof and/or a solvate thereof, wherein a is 1, which process comprises reacting a compound of formula (XVI):



(XVI)

wherein each of R'_1, R'_2, R'_3, R'_5, R'_6, and R'_7 is respectively R_1, R_2, R_3, R_5, R_6, or R_7 as defined above or a group convertible to R_1, R_2, R_3, R_5, R_6, or R_7 respectively as defined above providing R'_2 is not aromatic in character, and L_1 represents a halogen atom such as a bromine atom, with a compound of formula (XVII):



(XVII)

wherein Y is a group R'$_4$, where R'$_4$ is R_4 as defined in relation to formula (I) or a protected form thereof or a group convertible thereto; and thereafter as required removing any protecting group Y, for example by dehydrogenation, and replacing the protective group Y with a group R'$_4$; and thereafter carrying out one or more of the following optional steps:

(i) converting any one of R'_1, R'_2, R'_3, R'_4, R'_5, R'_6 and R'_7 to R_1, R_2, R_3, R_4, R_5, R_6 and R_7 respectively as required, to obtain a compound of formula (I);

(ii) converting a compound of formula (I) into another compound of formula (I); and

(iii) preparing a salt of the compound of formula (I) and/or a solvate thereof.

Protected forms of R_4 will vary according to the particular nature of the group being protected but will be chosen in accordance with normal chemical practice.

Groups convertible to R_4 include groups dictated by conventional chemical practice to be required and to be appropriate, depending upon the specific nature of the R_4 under consideration.

Suitable deprotection methods for deprotecting protected forms of R_4 and conversion methods for converting R'_4 to R_4 will be those used conventionally in the art depending upon the particular groups under consideration with reference to standard texts such as Greene, T.W. and Wuts, P.G.M. Protective Groups in Organic Synthesis, John Wiley & Sons Inc. New York, 1991 (Second Edt.) or in Kocienski, P.J. Protecting groups. George Thieme Verlag, New York, 1994 and Chemistry of the Amino Group, Patais (Ed.), Interscience, New York 1968; or Advanced Organic Chemistry, March J, John Wiley & Sons, New York, 1992.

Suitable groups convertible into other groups include protected forms of said groups.

Advantageously, a compound of formula (XVII) will be a compound of formula (V) as defined above.

Suitably R'_1, R'_2, R'_3, R'_4, R'_5, R'_6 and R'_7 each represents R_1, R_2, R_3, R_4, R_5, R_6 and R_7 respectively or a protected form thereof.

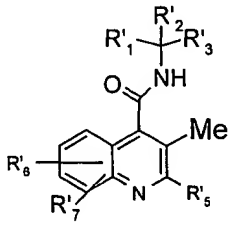
Suitable deprotection methods for deprotecting protected forms of R_1, R_2, R_3, R_4, R_5, R_6 and R_7 and conversion methods for converting R'_1, R'_2, R'_3, R'_4, R'_5, R'_6 and R'_7 to R_1, R_2, R_3, R_4, R_5, R_6 and R_7 respectively will be those used conventionally in the art depending upon the particular groups under consideration with reference to standard texts such as Greene, T.W. and Wuts, P.G.M. Protective Groups in Organic Synthesis, John Wiley & Sons Inc. New York, 1991 (Second Edt.) or in Kocienski, P.J. Protecting groups. George Thieme Verlag, New York, 1994 and

Chemistry of the Amino Group, Patais (Ed.), Interscience, New York 1968; or Advanced Organic Chemistry, March J, John Wiley & Sons, New York, 1992.

Suitably, reaction between the compounds of formulae (XVI) and (XVII) is carried out under conventional amination conditions, for example when L_1 is a bromine atom then the reaction is conveniently carried out in an aprotic solvent, such as tetrahydrofuran or dimethylformamide at any temperature providing a suitable rate of formation of the required product, usually at ambient temperature; preferably the reaction is carried out in the presence of triethylamine (TEA) or K_2CO_3.

The compounds of formula (XVII) are known, commercially available compounds or they can be prepared using methods analogous to those used to prepare known compounds; for example the methods described in the Chemistry of the Amino Group, Patais (Ed.), Interscience, New York 1968; Advanced Organic Chemistry, March J, John Wiley & Sons, New York, 1992 ; J. Heterocyclic Chem. (1990), 27, 1559; Synthesis (1975), 135, Bioorg. Med. Chem. Lett. (1997), 7, 555, or Protective Groups in Organic Synthesis (second edition), Wiley Interscience, (1991) or other methods mentioned herein.

A compound of formula (XVI) is prepared by appropriate halogenation of a compound of formula (XVIII):



(XVIII)

wherein R'_1, R'_2, R'_3, R'_5, R'_6, and R'_7 are as defined above in relation to formula (XVI).

Suitable halogenation reagents are conventional reagents depending upon the nature of the halogen atom required, for example when L_1 is bromine a preferred halogenation reagent is N-bromosuccinimide (NBS).

The halogenation of the compound of formula (XVIII) is carried out under conventional conditions, for example bromination is carried out by treatment with NBS in an inert solvent, such as carbon tetrachloride CCl_4, or 1,2-dichloroethane or CH_3CN, at any temperature providing a suitable rate of formation of the required product, suitably at an elevated temperature such as a temperature in the range of 60°C to 100°C, for example 80°C; preferably the reaction is carried out in the presence of a catalytic amount of benzoyl peroxide.

Suitably, the compound of formula (XVIII) may be prepared by reacting a compound of formula (VI) as defined above or an active derivative thereof with a compound of formula (III) as defined above wherein R'_2 is not aromatic in character.

It is favoured if the compound of formula (VI) is present in the reaction mix as an active derivative, as hereinbefore described.

The reaction between the compound of formula (VI) or the active derivative thereof and the compound of formula (III) is carried out under the appropriate conventional conditions for the particular compounds chosen. Generally, when the compound of formula (VI) is present as an active derivative the reaction is carried out using the same solvent and conditions as used to prepare the active derivative, preferably the active derivative is prepared *in situ* prior to forming the compound of formula (XVIII).

For example, the reaction between an active derivative of the compound of formula (VI) and the compound of formula (III) may be carried out:

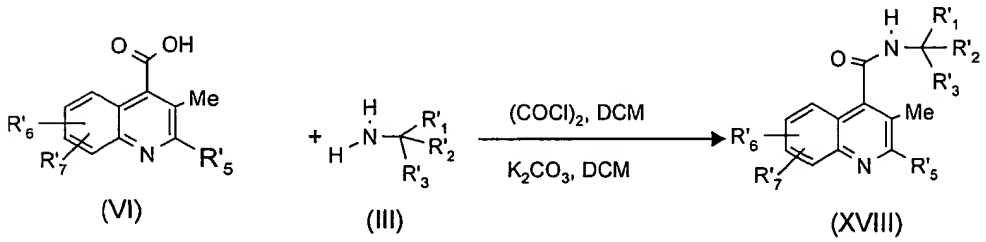
(a) by first preparing an acid chloride and then coupling said chloride with the compound of formula (III) in the presence of an inorganic or organic base in a suitable aprotic solvent such as dimethylformamide (DMF) at a temperature in a range from -70 to 50°C (preferably in a range from -10 to 20°C); or

(b) by treating the compound of formula (VI) with a compound of formula (III) in the presence of a suitable condensing agent, such as for example N,N'-carbonyl diimidazole (CDI) or a carbodiimide such as dicyclohexylcarbodiimide (DCC) or N-dimethylaminopropyl-N'-ethylcarbodiimide, preferably in the presence of N-

hydroxybenzotriazole (HOBT) to maximise yields and avoid racemization processes (see *Synthesis,* 453, 1972), or O-benzotriazol-1-yl-N,N,N',N'-tetramethyluroniumhexafluorophosphate (HBTU), in an aprotic solvent, such as a mixture of acetonitrile (MeCN) and tetrahydrofuran (THF), for example a mixture in a volume ratio of from 1:9 to 7:3 (MeCN:THF), at any temperature providing a suitable rate of formation of the required product, such as a temperature in the range of from -70 to 50°C, preferably in a range of from -10 to 25°C, for example at 0°C.

A preferred reaction is set out in Scheme 2 shown below:

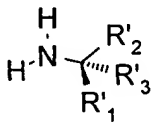
Scheme 2

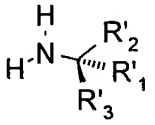


(VI) (III) (XVIII)

In the case in which the corresponding alkyl (such as methyl or ethyl) ester of compounds (VI) is utilised, a hydrolysis is required before conversion to compound (XVIII) in Scheme 2. Such hydrolysis can be carried out under acidic conditions, such 10-36% hydrochloric acid at a temperature in the range between 30 and 100 °C.

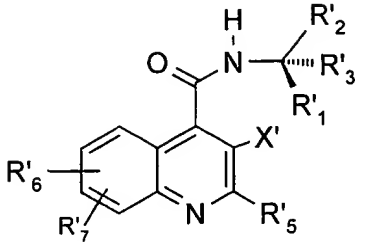
As hereinbefore mentioned, the compounds of formula (I) may exist in more than one stereoisomeric form - and the process of the invention may produce racemates as well as enantiomerically pure forms. Accordingly, a pure enantiomer of a compound of formula (I) can be obtained by reacting a compound of the above defined formula (II) with an appropriate enantiomerically pure primary amine of formula (IIIa) or (IIIc):

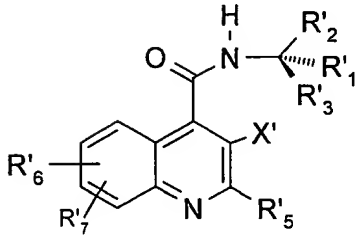




(IIIa) (IIIc)

wherein R'_1, R'_2 and R'_3 are as defined above, to obtain a compound of formula (I'a) or (I'c):

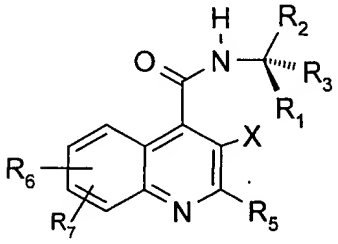


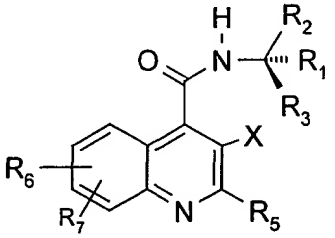


(I'a) (I'c)

wherein R'_1, R'_2, R'_3, X', R'_5, R'_6, and R'_7 are as defined above.

Compounds of formula (I'a) or (I'c) may subsequently be converted to compounds of formula (Ia) or (Ic) by the methods of conversion mentioned before:





(Ia) (Ic)

wherein R_1, R_2, R_3, X, R_5, R_6, and R_7 are as defined above.

Suitably, in the above mentioned compounds of formulae (Ia), (Ic), (I'a), (I'c), (IIIa) and (IIIc) R_1 represents hydrogen.

An alternative method for separating optical isomers is to use conventional, fractional separation methods in particular fractional crystallisation methods. Thus, a pure enantiomer of a compound of formula (I) is obtained by fractional crystallisation of a diastereomeric salt formed by reaction of the racemic compound of formula (I)

with an optically active strong acid resolving agent, such as camphosulphonic acid, tartaric acid, O,O'-di-p-toluoyltartaric acid or mandelic acid, in an appropriate alcoholic solvent, such as ethanol or methanol, or in a ketonic solvent, such as acetone. The salt formation process should be conducted at a temperature between 20°C and 80°C, preferably at 50°C.

A suitable conversion of one compound of formula (I) into a further compound of formula (I) involves converting one group X into another group X by for example:

(i) converting a ketal into a ketone, by such as mild acidic hydrolysis, using for example dilute hydrochloric acid;

(ii) reducing a ketone to a hydroxy group by use of a borohydride reducing agent;

(iii) converting a carboxylic ester group into a carboxyl group using basic hydrolysis; and/or

(iv) reducing a carboxylic ester group to a hydroxymethyl group, by use of a borohydride reducing agent.

As indicated above, where necessary, the conversion of any group R'_1, R'_2, R'_3, X', R'_5, R'_6, and R'_7 into R_1, R_2, R_3, X, R_5, R_6, and R_7 which as stated above are usually protected forms of R_1, R_2, R_3, X, R_5, R_6, or R_7 may be carried out using appropriate conventional conditions such as the appropriate deprotection procedure.

It will be appreciated that in any of the above mentioned reactions any reactive group in the substrate molecule may be protected and deprotected according to conventional chemical practice, for example as described by Greene, T.W. and Wuts, P.G.M. Protective Groups in Organic Synthesis, John Wiley & Sons Inc. New York, 1991 (Second Edt.) or in Kocienski, P.J. Protecting groups. George Thieme Verlag, New York, 1994.

Suitable protecting groups in any of the above mentioned reactions are those used conventionally in the art. Thus, for example suitable hydroxy protecting groups include benzyl or trialkylsilyl groups.

The methods of formation and removal of such protecting groups are those conventional methods appropriate to the molecule being protected. Thus for example a

benzyloxy group may be prepared by treatment of the appropriate compound with a benzyl halide, such as benzyl bromide, and thereafter, if required, the benzyl group may be conveniently removed using catalytic hydrogenation or a mild ether cleavage reagent such as trimethylsilyl iodide or boron tribromide.

As indicated above, the compounds of formula (I) have useful pharmaceutical properties.

Accordingly the present invention also provides a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, for use as an active therapeutic substance.

In particular, the present invention also provides a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, for the treatment or prophylaxis of the Primary and Secondary Conditions.

The present invention further provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier.

The present invention also provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for the treatment of the Primary and Secondary Conditions.

As mentioned above the Primary conditions include respiratory diseases, such as chronic obstructive pulmonary disease (COPD), asthma, airway hyper-reactivity, cough; inflammatory diseases such as inflammatory bowel disease, psoriasis, fibrositis, osteoarthritis, rheumatoid arthritis and inflammatory pain; neurogenic inflammation or peripheral neuropathy, allergies such as eczema and rhinitis; ophthalmic diseases such as ocular inflammation, conjunctivitis, vernal conjuctivitis and the like; cutaneous diseases, skin disorders and itch, such as cutaneous wheal and flare, contact dermatitis, atopic dermatitis, urticaria and other eczematoid dermatitis; adverse immunological reactions such as rejection of transplanted tissues and disorders related to immune enhancement or suppression such as systhemic lupus erythematosis; gastrointestinal (GI) disorders and diseases of the GI tract such as disorders associated with the neuronal control of viscera such as ulcerative colitis, Crohn's disease, irritable bowel

syndrome (IBS), gastro-exophageous reflex disease (GERD); urinary incontinence and disorders of the bladder function; renal disorders; increased blood pressure, proteinuria, coagulopathy and peripheral and cerebral oedema following pre-eclampsia in pregnancies.

As mentioned above, the Secondary conditions include disorders of the central nervous system such as anxiety, depression, psychosis and schizophrenia; neurodegenerative disorders such as AIDS related dementia, senile dementia of the Alzheimer type, Alzheimer's disease, Down's syndrome, Huntingdon's disease, Parkinson's disease, movement disorders and convulsive disorders (for example epilepsy); demyelinating diseases such as multiple sclerosis and amyotrophic lateral sclerosis and other neuropathological disorders such as diabetic neuropathy, AIDS related neuropathy, chemotherapy-induced neuropathy and neuralgia; addiction disorders such as alcoholism; stress related somatic disorders; reflex sympathetic dystrophy such as shoulder/hand syndrome; dysthymic disorders; eating disorders (such as food intake disease); fibrosing and collagen diseases such as scleroderma and eosinophilic fascioliasis; disorders of the blood flow caused by vasodilatation and vasospastic diseases such as angina, migraine and Reynaud's disease and pain or nociception, for example, that is attributable to or associated with any of the foregoing conditions especially the transmission of pain in migraine.

Such a medicament, and a composition of this invention, may be prepared by admixture of a compound of the invention with an appropriate carrier. It may contain a diluent, binder, filler, disintegrant, flavouring agent, colouring agent, lubricant or preservative in conventional manner.

These conventional excipients may be employed for example as in the preparation of compositions of known agents for treating the conditions.

Preferably, a pharmaceutical composition of the invention is in unit dosage form and in a form adapted for use in the medical or veterinarial fields. For example, such preparations may be in a pack form accompanied by written or printed instructions for use as an agent in the treatment of the conditions.

The suitable dosage range for the compounds of the invention depends on the compound to be employed and on the condition of the patient. It will also depend, inter alia, upon the relation of potency to absorbability and the frequency and route of administration.

The compound or composition of the invention may be formulated for administration by any route, and is preferably in unit dosage form or in a form that a human patient may administer to himself in a single dosage. Advantageously, the composition is suitable for oral, rectal, topical, parenteral, intravenous or intramuscular administration. Preparations may be designed to give slow release of the active ingredient.

Compositions may, for example, be in the form of tablets, capsules, sachets, vials, powders, granules, lozenges, reconstitutable powders, or liquid preparations, for example solutions or suspensions, or suppositories.

The compositions, for example those suitable for oral administration, may contain conventional excipients such as binding agents, for example syrup, acacia, gelatine, sorbitol, tragacanth, or polyvinylpyrrolidone; fillers, for example lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tabletting lubricants, for example magnesium stearate; disintegrants, for example starch, polyvinyl-pyrrolidone, sodium starch glycollate or microcrystalline cellulose; or pharmaceutically acceptable setting agents such as sodium lauryl sulphate.

Solid compositions may be obtained by conventional methods of blending, filling, tabletting or the like. Repeated blending operations may be used to distribute the active agent throughout those compositions employing large quantities of fillers. When the composition is in the form of a tablet, powder, or lozenge, any carrier suitable for formulating solid pharmaceutical compositions may be used, examples being magnesium stearate, starch, glucose, lactose, sucrose, rice flour and chalk. Tablets may be coated according to methods well known in normal pharmaceutical practice, in particular with an enteric coating. The composition may also be in the form of an ingestible capsule, for example of gelatine containing the compound, if desired with a carrier or other excipients.

Compositions for oral administration as liquids may be in the form of, for example, emulsions, syrups, or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid compositions may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, gelatine, hydroxyethylcellulose, carboxymethylcellulose, aluminium stearate gel, hydrogenated edible fats; emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; aqueous or non-aqueous vehicles, which include edible oils, for example almond oil, fractionated coconut oil, oily esters, for example esters of glycerine, or propylene glycol, or ethyl alcohol, glycerine, water or normal saline; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid; and if desired conventional flavouring or colouring agents.

The compounds of this invention may also be administered by a non-oral route. In accordance with routine pharmaceutical procedure, the compositions may be formulated, for example for rectal administration as a suppository. They may also be formulated for presentation in an injectable form in an aqueous or non-aqueous solution, suspension or emulsion in a pharmaceutically acceptable liquid, e.g. sterile pyrogen-free water or a parenterally acceptable oil or a mixture of liquids. The liquid may contain bacteriostatic agents, anti-oxidants or other preservatives, buffers or solutes to render the solution isotonic with the blood, thickening agents, suspending agents or other pharmaceutically acceptable additives. Such forms will be presented in unit dose form such as ampoules or disposable injection devices or in multi- dose forms such as a bottle from which the appropriate dose may be withdrawn or a solid form or concentrate which can be used to prepare an injectable formulation.

The compounds of this invention may also be administered by inhalation, via the nasal or oral routes. Such administration can be carried out with a spray formulation comprising a compound of the invention and a suitable carrier, optionally suspended in, for example, a hydrocarbon propellant.

Preferred spray formulations comprise micronised compound particles in combination with a surfactant, solvent or a dispersing agent to prevent the

sedimentation of suspended particles. Preferably, the compound particle size is from about 2 to 10 microns.

A further mode of administration of the compounds of the invention comprises transdermal delivery utilising a skin-patch formulation. A preferred formulation comprises a compound of the invention dispersed in a pressure sensitive adhesive which adheres to the skin, thereby permitting the compound to diffuse from the adhesive through the skin for delivery to the patient. For a constant rate of percutaneous absorption, pressure sensitive adhesives known in the art such as natural rubber or silicone can be used.

As mentioned above, the effective dose of compound depends on the particular compound employed, the condition of the patient and on the frequency and route of administration. A unit dose will generally contain from 20 to 1000 mg and preferably will contain from 30 to 500 mg, in particular 50, 100, 150, 200, 250, 300, 350, 400, 450, or 500 mg. The composition may be administered once or more times a day for example 2, 3 or 4 times daily, and the total daily dose for a 70 kg adult will normally be in the range 100 to 3000 mg. Alternatively the unit dose will contain from 2 to 20 mg of active ingredient and be administered in multiples, if desired, to give the preceding daily dose.

No unacceptable toxicological effects are expected with compounds of the invention when administered in accordance with the invention.

The present invention also provides a method for the treatment and/or prophylaxis of the Primary and Secondary Conditions in mammals, particularly humans, which comprises administering to the mammal in need of such treatment and/or prophylaxis an effective, non-toxic pharmaceutically acceptable amount of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof.

The activity of the compounds of the present invention, as NK_3 ligands, is determined by their ability to inhibit the binding of the radiolabelled NK_3 ligands, [^{125}I]-[Me-Phe^7]-NKB or [^{3}H]-Senktide, to guinea-pig and human NK_3 receptors

(Renzetti et al, **1991**, *Neuropeptide, 18*, 104-114; Buell et al, **1992**, *FEBS, 299(1)*, 90-95; Chung et al, **1994**, *Biochem. Biophys. Res. Commun., 198(3)*, 967-972).

The binding assays utilised allow the determination of the concentration of the individual compound required to reduce by 50% the [^{125}I]-[Me-Phe^{7}]-NKB and [^{3}H]-Senktide specific binding to NK_3 receptor in equilibrium conditions (IC50).

Binding assays provide for each compound tested a mean IC_{50} value of 2-5 separate experiments performed in duplicate or triplicate. The most potent compounds of the present invention show IC_{50} values in the range 0.1-1000 nM. The NK_3-antagonist activity of the compounds of the present invention is determined by their ability to inhibit senktide-induced contraction of the guinea-pig ileum (Maggi et al, **1990**, *Br. J. Pharmacol., 101*, 996-1000) and rabbit isolated iris sphincter muscle (Hall et al., **1991**, *Eur. J. Pharmacol., 199*, 9-14) and human NK_3 receptors-mediated Ca^{++} mobilisation (Mochizuki et al, **1994**, *J. Biol. Chem., 269*, 9651-9658). Guinea-pig and rabbit *in-vitro* functional assays provide for each compound tested a mean K_B value of 3-8 separate experiments, where K_B is the concentration of the individual compound required to produce a 2-fold rightward shift in the concentration-response curve of senktide. Human receptor functional assay allows the determination of the concentration of the individual compound required to reduce by 50% (IC_{50} values) the Ca^{++} mobilisation induced by the agonist NKB. In this assay, the compounds of the present invention behave as antagonists.

The activity of the compounds of the present invention, as NK-2 ligands, is determined by their ability to inhibit the binding of the radiolabelled NK-2 ligands, [^{125}I]-NKA or [^{3}H]-NKA, to human NK-2 receptors (Aharony et al, **1992**, *Neuropeptide, 23*, 121-130).

The binding assays utilised allow the determination of the concentration of the individual compound required to reduce by 50% the [^{125}I]-NKA and [^{3}H]-NKA specific binding to NK2 receptor in equilibrium conditions (IC_{50}).

Binding assays provide for each compound tested a mean IC_{50} value of 2-5 separate experiments performed in duplicate or triplicate. The most potent compounds of the present invention show IC_{50} values in the range 0.5-1000 nM, such as 1-1000 nM. The NK-2-antagonist activity of the compounds of the present invention is determined by their ability to inhibit human NK-2 receptor-mediated Ca^{++} mobilisation (Mochizuki et al, **1994**, *J. Biol. Chem., 269*, 9651-9658). Human receptor functional assay allows the determination of the concentration of the individual compound required to reduce by 50% (IC_{50} values) the Ca^{++} mobilisation induced by the agonist NKA. In this assay, the compounds of the present invention behave as antagonists.

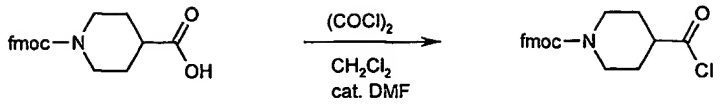
The therapeutic potential of the compounds of the present invention in treating the conditions can be assessed using rodent disease models.

As stated above, the compounds of formula (I) are also considered to be useful as diagnostic tools. Accordingly, the invention includes a compound of formula (I) for use as diagnostic tools for assessing the degree to which neurokinin-3 and neurokinin-2 receptor activity (normal, overactivity or underactivity) is implicated in a patient's symptoms. Such use comprises the use of a compound of formula (I) as an antagonist of said activity, for example including but not restricted to Tachykinin agonist-induced inositol phosphate turnover or electrophysiological activation, of a cell sample obtained from a patient. Comparison of such activity in the presence or absence of a compound of formula (I), will disclose the degree of NK-3 and NK-2 receptor involvement in the mediation of agonist effects in that tissue.

The following Descriptions illustrate the preparation of the intermediates, whereas the following Examples illustrate the preparation of the compounds of the invention.

Descriptions and Examples

DESCRIPTION 1 : **4-Chlorocarbonyl-piperidine-1-carboxylic acid 9H-fluoren-9-ylmethyl ester**



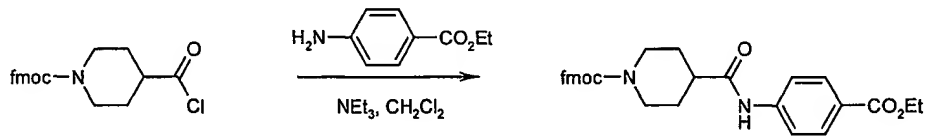
A solution of 0.6 ml (6.83 mmol) of oxalyl chloride in 10 ml methylene chloride was added dropwise to a solution of 2.0 g (5.69 mmol) of fmoc-isonipecotic acid and 2 drops of DMF in 50 ml methylene chloride, at room temperature.

When the gas evolution had ceased the mixture was concentrated, taken-up in dry cyclohexane, concentrated again and used in the next step without further purification.

$C_{21}H_{20}ClNO_3$

MW = 369.85

DESCRIPTION 2 : **4-(4-Ethoxycarbonyl-phenylcarbamoyl)-piperidine-1-carboxylic acid 9H-fluoren-9-ylmethyl ester**



A solution of crude 4-chlorocarbonyl-piperidine-1-carboxylic acid 9H-fluoren-9-ylmethyl ester (max 1.42 mmol) (compound of Description 1) in 6 ml methylene chloride was added dropwise to a solution of 0.25 g (1.49 mmol) of 4-amino ethylbenzoate and 22 microliters of triethylamine in 15 ml methylene chloride. The mixture was stirred one hour at room temperature, then washed with water, dried over $MgSO_4$ and concentrated. The residue was triturated in isopropyl ether, then purified by flash chromatography over 60 g silicagel (eluent: CH_2Cl_2/MeOH : 98/2), affording 0.596 g (85% over the two steps) of white crystals.

$C_{30}H_{30}N_2O_5$

MW = 498.58

200MHz ^{1}H-NMR (CDCl3): 1.39(t,3H); 1.65-2.04(m,4H); 2.43(tt,1H); 2.86(m,2H); 4.00-4.55(m,7H); 7.22-7.47(4Har); 7.50-7.67(m,5H); 7.77(d,2Har); 8.01(d,2Har)ppm.

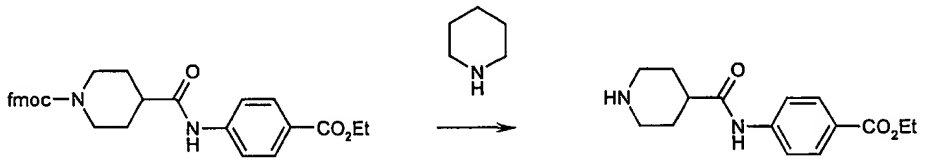
DESCRIPTION 3 : **4-(3-Ethoxycarbonyl-phenylcarbamoyl)-piperidine-1-carboxylic acid 9H-fluoren-9-ylmethyl ester**

Prepared following procedure of Description 2 from the compound of Description 1 and 3-amino ethylbenzoate.

$C_{30}H_{30}N_2O_5$

MW = 498.58

DESCRIPTION 4 : **4-[(1-Piperidin-4-yl-methanoyl)-amino]-benzoic acid ethyl ester.**



A mixture of 0.564 g (1.12 mmol) of 4-(4-ethoxycarbonyl-phenylcarbamoyl)-piperidine-1-carboxylic acid 9H-fluoren-9-ylmethyl ester (compound of Description 2), 0.16 ml piperidine and 23 ml acetonitrile was stirred 48 h at room temperature. The solvent was concentrated and the residue purified by flash chromatography over 40 g of silicagel (eluent: CH_2Cl_2/MeOH/NH_4OH : 90/10/1). Concentration and drying of the desired fractions afforded 0.17 g (54%) of the title compound.

$C_{15}H_{20}N_2O_3$

MW = 276.33

200MHz ^{1}H-NMR (CDCl3): 1.38(t,3H); 1.58-2.10(m,5H); 2.41(m,1H); 2.66(m,2H); 3.19(m,2H); 4.35(q,2H); 7.50(broad band,1H); 7.61(d,2Har); 8.00(d,2Har)ppm.

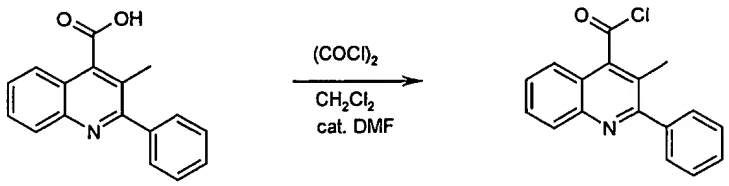
DESCRIPTION 5 : **3-[(1-Piperidin-4-yl-methanoyl)-amino]-benzoic acid ethyl ester.**

Prepared following the procedure of Description 4 starting from compound of Description 3

$C_{15}H_{20}N_2O_3$

MW = 276.33

DESCRIPTION 6 : **3-Methyl-2-phenyl-quinoline-4-carbonyl chloride**

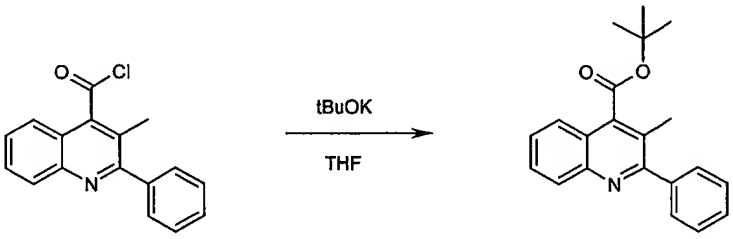


A solution of 14.35 g (54.5 mmol) of 3-methyl-2-phenyl-quinoline-4-carboxylic acid and one drop of DMF in 100 ml methylene chloride was treated dropwise with 6.92 g (54.5 mmol) oxalyl chloride. After the end of the gas evolution the mixture was concentrated to dryness and used in the next step without further purification.

$C_{17}H_{12}ClNO$

MW = 281.74

DESCRIPTION 7 : **3-Methyl-2-phenyl-quinoline-4-carboxylic acid tert.-butyl ester**



The crude acid chloride obtained in Description 6 was dissolved in 100 ml anhydrous THF and filtered. This solution was added dropwise to a solution of 6.12 g (5.45 mmol) potassium terbutylate in 100 ml anhydrous THF and stirred for 16 h. The reaction mixture was neutralised with acetic acid and the solvent concentrated. The residue was dissolved in AcOEt and the organic phase was washed with water and dried over $MgSO_4$. After concentration to dryness the residue was dissolved in heptane and

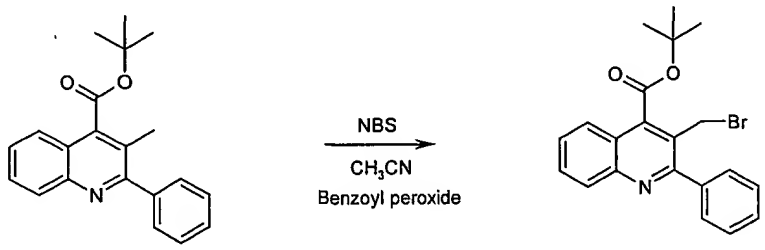
filtered. The mother liquors were then purified by flash chromatography over silicagel (eluent: heptane/CH_2Cl_2: 1/2) affording 3.0 g (17.2%) of the title compound..

$C_{21}H_{21}NO_2$

MW = 319.40

200MHz ^{1}H-NMR (CDCl3): 1.72(s,9H); 2.42(s,3H); 7.40-7.88(m,8Har); 8.15(d,1Har)ppm.

DESCRIPTION 8 : **3-Bromomethyl-2-phenyl-quinoline-4-carboxylic acid tert.-butyl ester**



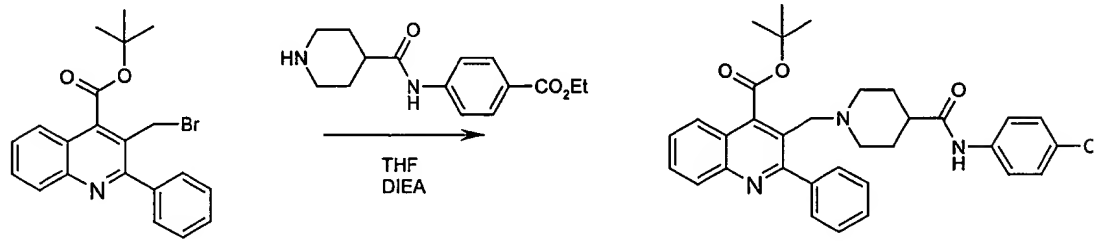
A solution of 3 g (9.4 mmol) of 3-methyl-2-phenyl-quinoline-4-carboxylic acid tert.-butyl ester (compound of Description 7) and 0.3 g of benzoyl peroxide in 100 ml acetonitrile was heated to reflux and 3.34 g (18.8 mmol) NBS were then added portionwise. The reflux was maintained one night, then the solvent was concentrated and the residue was triturated with 50 ml carbon tetrachloride and filtered. The filtrate was diluted with 50 ml methylene chloride and the organic phase was washed with water, a solution of $NaHCO_3$, again with water, dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography on silicagel (eluent: methylene chloride/heptane : 3/1) to afford 3 g (80%) of the title compound as an oil.

$C_{21}H_{20}BrNO_2$

MW = 398.30

200MHz ^{1}H-NMR (CDCl3): 1.77(s,9H); 4.67(s,2H); 7.40-7.85(7Har); 7.89(d,1Har); 8.14(d,1Har)ppm.

DESCRIPTION 9 : **3-[4-(4-Ethoxycarbonyl-phenylcarbamoyl)-piperidin-1-ylmethyl]-2-phenyl-quinoline-4-carboxylic acid tert-butyl ester**



A solution of 0.21 g 3-bromomethyl-2-phenyl-quinoline-4-carboxylic acid tert-butyl ester (compound of Description 8), 0.16 g (0.579 mmol) 4-[(1-piperidin-4-yl-methanoyl)-amino]-benzoic acid ethyl ester (compound of Description 4), 120 microliters (1.1 equivalent) DIEA in 20 ml THF was stirred at room temperature for 19 h.. The mixture was concentrated, re-dissolved in CH_2Cl_2 and washed with water. After drying over $MgSO_4$ the organic phase was concentrated and the residue was purified by flash chromatography over 25 g silicagel (eluent: CH_2Cl_2/MeOH: 98/2) affording 350 mg of the desired compound but with unsatisfactory purity. A second chromatography over 20 g silicagel (eluent: Heptane/AcOEt:2/1) afforded 250 mg (80%) of a white crystalline title compound.

$C_{36}H_{39}N_3O_5$

MW = 593.72

200MHz ^{1}H-NMR (CDCl3): 1.37(t,3H); 1.73(s,9H); 1.50-2.25(7H); 2.75(m,2H); 3.67(m,2H); 4.35(q,2H); 7.48-7.65(m,8Har); 7.74(m,1Har); 7.85-8.05(m,3Har); 8.15(d,1Har)ppm.

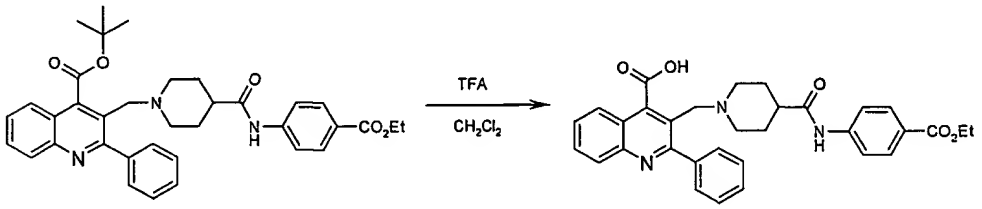
DESCRIPTION 10 : **3-[4-(3-Ethoxycarbonyl-phenylcarbamoyl)-piperidin-1-ylmethyl]-2-phenyl-quinoline-4-carboxylic acid tert-butyl ester**

Prepared following procedure of Description 9 starting from compound of Description 8 and compound of Description 5

$C_{36}H_{39}N_3O_5$

MW = 593.72

DESCRIPTION 11: **3-[4-(4-Ethoxycarbonyl-phenylcarbamoyl)-piperidin-1-ylmethyl]-2-phenyl-quinoline-4-carboxylic acid**



A mixture of 0.24 g (0.4 mmol) of 3-[4-(4-ethoxycarbonyl-phenylcarbamoyl)-piperidin-1-ylmethyl]-2-phenyl-quinoline-4-carboxylic acid tert-butyl ester (compound of Description 9), 3 ml of methylene chloride and 1.3 ml trifluoroacetic acid (TFA) was stirred at room temperature for 3 h. The solvent was concentrated and the residue triturated with diethyl ether. The mixture was filtered and the solid was dried in vacuo to afford 0.23 g of the title compounds.

$C_{32}H_{31}N_3O_5$

MW = 537.61

200MHz ^{1}H-NMR (CDCl3): 1.36(t,3H); 2.03(m,4H); 2.42-3.55(m,5H); 4.33(q,2H); 4.51(s,2H); 5.70(broad band,xH); 7.40-8.02(m,11Har); 8.25(d,2Har); 9.10(broad band,1H)ppm.

DESCRIPTION 12: **3-[4-(3-Ethoxycarbonyl-phenylcarbamoyl)-piperidin-1-ylmethyl]-2-phenyl-quinoline-4-carboxylic acid**

Prepared from compound of Description 10 and following the procedure of Description 11.

$C_{32}H_{31}N_3O_5$

MW = 537.61

DESCRIPTION 13: **3-Methyl-2-phenyl-quinoline-4-carboxylic acid ((S)-1-cyclohexyl-ethyl)-amide**

4-Carboxy-3-methyl-2-phenylquinoline (40 g, 0.152 mol) (CAS [43071-45-0]) was suspended in CH_2Cl_2 (600 ml) and oxalyl chloride (6.6 ml, 0.311 mol) was added dropwise at 0° C under magnetic stirring. After 15 min 2 drops of DMF were added. The reaction was vigorous with gas evolution. The mixture was stirred at room temperature until the solid was completely dissolved (about 2 h). The solution was evaporated. The crude material was redissolved in CH_2Cl_2 (150 ml) and slowly dropped into a suspension of K_2CO_3 (47 g) and (S)-1-cyclohexylethyl amine (29 ml, 0.196 mol) in CH_2Cl_2 (250 ml) maintaining the temperature between 10-15°C. The dark solution was left 1 h at room temperature. and 1 h refluxing. The organic phase was then washed with water, NaOH 1N, brine, dried over Na_2SO_4 and then evaporated under vacuum. The crude residue was triturated with AcOEt. After filtration 46.6 g of the title compound were obtained, mp = 177-180°C. Yield: 82 %

$C_{25}H_{28}N_2O$

MW = 372.51

$[\alpha]_D$ = +21.77 (c = 0.4 in MeOH).

DESCRIPTION 14: **3-Bromomethyl-2-phenyl-quinoline-4-carboxylic acid ((S)-1-cyclohexyl-ethyl)-amide**

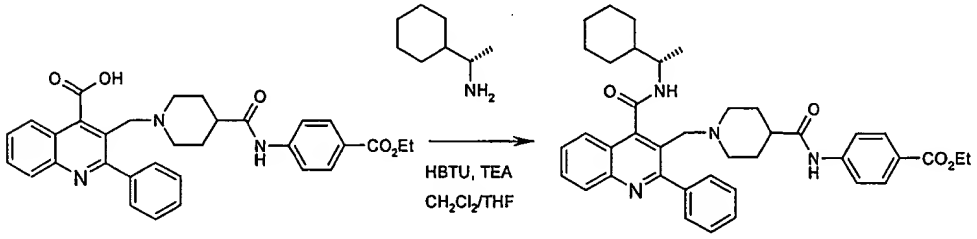
3-Methyl-2-phenyl-quinoline-4-carboxylic acid ((S)-1-cyclohexyl-ethyl)-amide (9.8 g, 26 mmol; compound prepared as in Description 13) and N-bromosuccinimmide (9.8 g, 55 mmol) were suspended in CCl_4 (100 ml) and warmed to incipient reflux. Dibenzoyl peroxide (about 300 mg) was carefully added portionwise and the solution was then refluxed for 2 h. The solvent was removed under vacuum and the residue was re-dissolved in CH_2Cl_2 (200 ml) and filtered. DCM was then evaporated and the residue was dissolved in AcOEt and washed with a saturated solution of $NaHCO_3$, brine, dried over Na_2SO_4, filtered and evaporated to give 6.9 g of the title compound as a white powder that were in the next step used without further purification, mp: 182-184°C. Yield: 58%

$C_{25}H_{27}BrN_2O$

MW = 451.41

$[\alpha]_D$ = -5.76 (c= 0.5 in CH_2Cl_2)

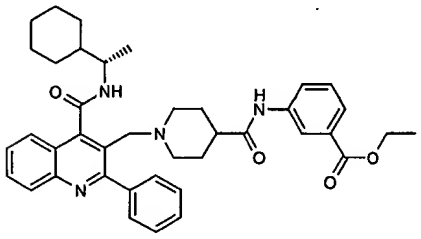
EXAMPLE 1: **4-[(1-{1-[4-((S)-1-Cyclohexyl-ethylcarbamoyl)-2-phenyl-quinolin-3-ylmethyl]-piperidin-4-yl}-methanoyl)-amino]-benzoic acid ethyl ester.**



A mixture of 0.2 g (0.4 mmol) of 3-[4-(4-ethoxycarbonyl-phenylcarbamoyl)-piperidin-1-ylmethyl]-2-phenyl-quinoline-4-carboxylic acid (compound of Description 11), 220 microliters (1.6 mmol) triethylamine, 0.23 g (0.6 mmol) HBTU, 10 ml anhydrous THF, 70 microliters (0.48 mmol) (S)-(+)-1-cyclohexylethylamine and 8 ml methylene chloride was stirred 16 h. at room temperature. The mixture was concentrated and the residue was dissolved in AcOEt. The organic phase was washed with water, then with 0.5N NaOH and again with water. After drying over $MgSO_4$ and concentration, the

residue was purified by flash chromatography over 28 g silica gel (eluent: heptane/AcOEt:1/1) affording 0.24 g (90%) of white crystals.

EXAMPLE 2: **3-[(1-{1-[4-((S)-1-Cyclohexyl-ethylcarbamoyl)-2-phenyl-quinolin-3-ylmethyl]-piperidin-4-yl}-methanoyl)-amino]-benzoic acid ethyl ester**



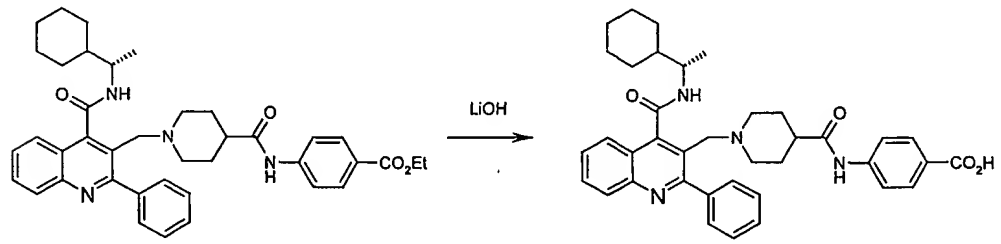
Following the procedure described for Example 1, starting from 3-[4-(3-Ethoxycarbonyl-phenylcarbamoyl)-piperidin-1-ylmethyl]-2-phenyl-quinoline-4-carboxylic acid (compound of Description 12) afforded the title compound as white crystals.

$C_{40}H_{46}N_4O_4$

MW = 646.83

M.P. = 128-130°C.

EXAMPLE 3 : **4-[(1-{1-[4-((S)-1-Cyclohexyl-ethylcarbamoyl)-2-phenyl-quinolin-3-ylmethyl]-piperidin-4-yl}-methanoyl)-amino]-benzoic acid.**

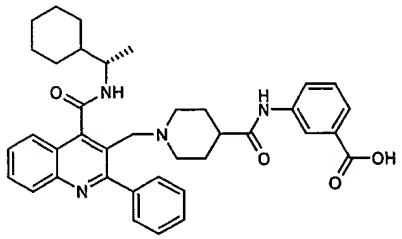


A mixture of 200 mg (0.31 mmol) of 4-[(1-{1-[4-((S)-1-cyclohexyl-ethylcarbamoyl)-2-phenyl-quinolin-3-ylmethyl]-piperidin-4-yl}-methanoyl)-amino]-benzoic acid ethyl ester (Example 1), 0.37 ml 1N LiOH and 25 ml ethanol was stirred for 24 h at room

temperature. The hydrolyse being not finished, 0.62 ml of 1N LiOH were added and the reaction was left stirring for 48 hours. The solvent was concentrated and the residue treated with 10 ml of a saturated solution oh $KHSO_4$ (ca 1 g in 20 ml water), then extracted with 30 ml AcOEt. The organic phase was washed with water, dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography over silicagel (eluent : CH_2Cl_2/MeOH: 9/1). A second column was performed on 15 g silicagel (eluent : CH_2Cl_2/MeOH: 95/5) affording 42 mg (22%) of the desired compounds as yellow crystals.

$C_{38}H_{42}N_4O_4$
MW = 618.77
M.P. = 207-208°C.

EXAMPLE 4 : **3-[(1-{1-[4-((S)-1-Cyclohexyl-ethylcarbamoyl)-2-phenyl-quinolin-3-ylmethyl]-piperidin-4-yl}-methanoyl)-amino]-benzoic acid**



Prepared as described in Example 3 starting from 3-[(1-{1-[4-((S)-1-cyclohexyl-ethylcarbamoyl)-2-phenyl-quinolin-3-ylmethyl]-piperidin-4-yl}-methanoyl)-amino]-benzoic acid ethyl ester (compound of Example 2) affording the title compound as beige crystals.

$C_{38}H_{42}N_4O_4$
MW = 618.77
M.P. = 230-232°C.

EXAMPLES 5 and 6 were prepared following the same synthetic pathway of Example1 starting from 1-(4-piperidinylcarbonyl)-pyrrolidine (RN 35090-95-0).
EXAMPLES 7 and 8 were prepared following the same synthetic pathway of Examples 1 and 3, respectively, starting from 4-ethoxycarbonylpiperidine.

EXAMPLES 9 AND 11: **3-Aminomethyl-2-phenyl-quinoline-4-carboxylic acid ((S)-1-cyclohexyl-ethyl)-amide derivatives**

A solution of 3-bromomethyl-2-phenyl-quinoline-4-carboxylic acid ((S)-1-cyclohexyl-ethyl)-amide (1 mmol, 0.45 g; compound prepared as in Description 14), 1.5 mmol of amine and ethyldiisopropylamine (3 mmol, 0.5 ml) in dry THF (15 ml) was stirred for 24 h at room temperature. The solvent was evaporated to dryness in vacuo and the residue was re-dissolved in AcOEt. This mixture was washed with a dilute NaOH solution, with water and dried over Na_2SO_4. After evaporating to dryness, the residue was purified by flash chromatography to afford the desired compound.

EXAMPLE 10: **1-[4-((S)-1-Cyclohexyl-ethylcarbamoyl)-2-phenyl-quinolin-3-ylmethyl]-piperidine-4-carboxylic acid**

1-[4-((S)-1-Cyclohexyl-ethylcarbamoyl)-2-phenyl-quinolin-3-ylmethyl]-piperidine-4-carboxylic acid methyl ester (0.21 g, 0.41 mmol), prepared as in Example 2, was dissolved in 6M HCl and refluxed for 4h. The solution was evaporated under vacuum to dryness and the residue was triturated with Et_2O. The yellow solid was filtered obtaining 160 mg of the title compound as hydrochloride salt, mp = 206-215°C.
$[\alpha]_D$ = +11.82 (c= 0.5 in MeOH)

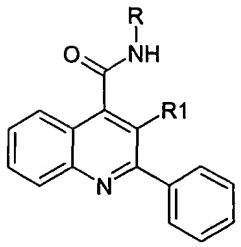


TABLE 1

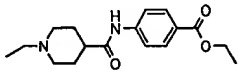
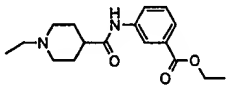
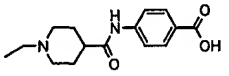
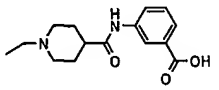
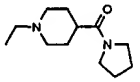
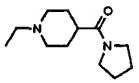
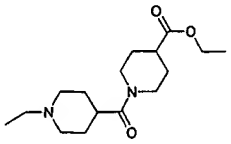
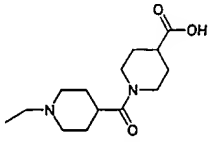
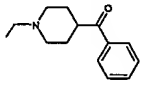
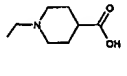
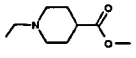
Ex.	R	R_1	Molecular Formula	Molecular Weight	Melting Point (°C)
1			$C_{40}H_{46}N_4O_4$	646.83	160-162
2			$C_{40}H_{46}N_4O_4$	646.83	128-130
3			$C_{38}H_{42}N_4O_4$	618.77	207-208
4			$C_{38}H_{42}N_4O_4$	618.77	230-232
5			$C_{35}H_{44}N_4O_2$	552.76	131-132
6			$C_{35}H_{38}N_4O_2$	546.71	135-136
7			$C_{39}H_{50}N_4O_4$	638.85	138-144
8			$C_{37}H_{46}N_4O_4$	610.79	190-195 (dec)
9			$C_{37}H_{41}N_3O_2$		
10			$C_{31}H_{37}N_3O_3$. HCl		206-215
11			$C_{32}H_{39}N_3O_3$		

TABLE 2

^{1}H NMR data of compounds of Examples of Table 1

Ex.	^{1}H NMR (Solvent) ppm and/or MS
1	(CDCl3) : 1.00-2.22(m,24H); 2.60(1H); 2.81(m,1H); 3.73(m,2H); 4.27(m,1H); 4.34(q,2H); 7.31(s,1H); 7.40-7.82(m,10Har); 7.97(d,2Har); 8.08(d,1H); 8.14(d,1Har)
2	(CDCl3): 1.00-2.20(m,23H); 2.60(m,1H); 2.80(m,1H); 3.71(dd,2H); 4.18-4.44(m,3H); 7.22(d,1H); 7.32(t,1Har); 7.48(m,5Har); 7.56(t,1Har); 7.67-8.00(m,6H); 8.11(m,2Har)
3	(DMSO-d_6) : 0.90-1.95(m,20H); 2.21(m,1H); 2.53(m,2H); 3.34(broad band,1H); 3.56(s,2H); 4.04(m,1H); 7.38-7.92(m,12Har); 8.03(d,1Har); 8.58(d,1H); 10.07(s,1H)
4	(CDCl3) : 0.95-2.00(m,15H); 1.21(d,3H); 2.17(m,1H); 2.51(m,2H); 3.37(m,3H); 3.56(s,2H); 4.02(m,1H); 7.29(t,1H); 7.38-7.95(10H); 8.03(d,1Har); 8.15(s,1Har); 8.60(d,br,1H); 9.90(br,1H)
5	(CDCl3) : 0.95-2.00(m,21H); 1.31(d,3H); 2.18(m,1H); 2.58(m,1H); 2.82(m,1H); 3.38(q,4H); 3.75(dd,2H); 4.28(m,1H); 7.48(m,5Har); 7.54(td,1Har); 7.73(td,1Har); 8.12(dd,2Har); 8.19(br,1H)
6	(CDCl3) : 1.20-1.98(m,10H); 1.70(d,3H); 2.19(m,2H); 2.60(m,1H);3.20-3.45(2t,4H); 3.60(m,2H); 5.60(m,1H); 7.20-7.63(m,11Har); 7.72(td,1Har); 7.99-8.18(m,2Har); 8.98(br,1H)
7	(CDCl3) : 0.95-2.00(m,27H); 2.32(m,1H); 2.41-2.88(m,4H); 3.04(m,1H); 3.72(m,3H); 4.02-4.45(m,3H); 7.48(m,5Har); 7.58(t,1Har); 7.73(t,1Har); 8.00(br,1H); 8.11(2d,2Har)
8	(CDCl3) : 0.92-2.12(m,24 H); 2.22-3.15(m,7H); 3.57-3.92(m,3H); 4.00(b,1H); 4.13-4.49(m,2H); 7.49(m,5Har); 7.59(t,1Har); 7.70(t,1Har); 7.97(br,1H); 8.06(d,1Har); 8.13(d,1Har)
9	ESI POS; AQA ; solvent: MeOH/ spray 3 kV / skimmer: 20 V/ probe 135°C: 560 (MH+)
10	^{1}H NMR (DMSO as sodium salt) δ: 8.51 (d br, 1H); 8.01 (d, 1H); 7.83 (d, 1H); 7.77 (dd, 1H); 7.64 (dd, 1H); 7.55 (m, 2H); 7.46 (m, 3H); 4.00 (m, 1H); 3.52 (s, 2H); 2.41 (m, 2H); 1.92 (m, 1H); 1.85-1.39 (m, 9H); 1.32-0.99 (m, 8H); 1.16 (d, 3H).

Ex.	^{1}H NMR (Solvent) ppm and/or MS
	ESI POS; AQA ; solvent: MeOH/ spray 3 kV / skimmer: 20 V/ probe 135°C: 500 (MH+)
11	^{1}H NMR (DMSO) δ: 8.27 (d br, 1H); 8.01 (d, 1H); 7.86 (d, 1H); 7.75 (dd, 1H); 7.62 (dd, 1H); 7.55 (m, 2H); 7.46 (m, 3H); 4.03 (m, 1H); 3.58 (s, 2H); 3.56 (s, 3H); 2.45 (m, 2H); 2.15 (m, 1H); 1.90-1.71 (m, 6H); 1.69-1.45 (m, 4H);1.37-1.08 (m, 7H); 1.20 (d, 3H). ESI POS; AQA ; solvent: MeOH/ spray 3 kV / skimmer: 20 V/ probe 135°C: 514 (MH+)

TABLE 3

Chemical names of parent compounds of Examples of Table 1 (names generated by Beilstein's Autonom)

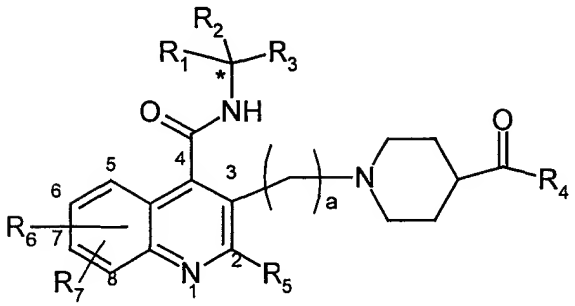
Example	Chemical name
1	2-Phenyl-3-[4-(1-pyrrolidin-1-yl-methanoyl)-piperidin-1-ylmethyl]-quinolin-4-carboxylic acid ((S)-1-phenyl-ethyl)-amide
1	4-[(1-{1-[4-((S)-1-Cyclohexyl-ethylcarbamoyl)-2-phenyl-quinolin-3-ylmethyl]-piperidin-4-yl}-methanoyl)-amino]-benzoic acid ethyl ester
2	3-[(1-{1-[4-((S)-1-Cyclohexyl-ethylcarbamoyl)-2-phenyl-quinolin-3-ylmethyl]-piperidin-4-yl}-methanoyl)-amino]-benzoic acid ethyl ester
3	4-[(1-{1-[4-((S)-1-Cyclohexyl-ethylcarbamoyl)-2-phenyl-quinolin-3-ylmethyl]-piperidin-4-yl}-methanoyl)-amino]-benzoic acid
4	3-[(1-{1-[4-((S)-1-Cyclohexyl-ethylcarbamoyl)-2-phenyl-quinolin-3-ylmethyl]-piperidin-4-yl}-methanoyl)-amino]-benzoic acid
5	2-Phenyl-3-[4-(1-pyrrolidin-1-yl-methanoyl)-piperidin-1-ylmethyl]-quinoline-4-carboxylic acid ((S)-1-cyclohexyl-ethyl)-amide
6	2-Phenyl-3-[4-(1-pyrrolidin-1-yl-methanoyl)-piperidin-1-ylmethyl]-quinolin-4-carboxylic acid ((S)-1-phenyl-ethyl)-amide

Example	Chemical name
7	1-(1-{-1-[4-((S)-1-Cyclohexyl-ethylcarbamoyl)-2-phenyl-quinolin-3-ylmethyl]-piperidin-4-yl}-methanoyl)-piperidine-4-carboxylic acid ethyl ester
8	1-(1-{-1-[4-((S)-1-Cyclohexyl-ethylcarbamoyl)-2-phenyl-quinolin-3-ylmethyl]-piperidin-4-yl}-methanoyl)-piperidine-4-carboxylic acid
9	2-Phenyl-3-[4-(1-phenyl-methanoyl)-piperidin-1-ylmethyl]-quinoline-4-carboxylic acid ((S)-1-cyclohexyl-ethyl)-amide
10	1-[4-((S)-1-Cyclohexyl-ethylcarbamoyl)-2-phenyl-quinolin-3-ylmethyl]-piperidine-4-carboxylic acid
11	1-[4-((S)-1-Cyclohexyl-ethylcarbamoyl)-2-phenyl-quinolin-3-ylmethyl]-piperidine-4-carboxylic acid methyl ester

5

CLAIMS

1 A compound of formula (I) below or a pharmaceutically acceptable salt or hydrate thereof:



(I)

wherein:

R_1 is H or alkyl;

R_2 is aryl or cycloalkyl or heteroaryl;

R_3 is H or alkyl, optionally substituted by one or more fluorines;

R_4 is $-NR_8R_9$ or R_{12};

R_8 is H or methyl;

R_9 is H, alkyl, aryl, cycloalkyl or $R_{10}R_{11}$; or R_8 and R_9 together form a heterocyclic ring comprising 3-8 ring members, which heterocyclic ring is optionally unsubstituted or is substituted one or more times by R_{11};

R_{10} is alkyl, aryl or cycloalkyl;

R_{11} is carboxy or alkylcarboxy;

R_{12} is R_{13} or OR_{13};

R_{13} is H or alkyl or aryl, optionally substituted by one or more fluorines;

R_5 is branched or linear alkyl, cycloalkyl, cycloalkylalkyl, aryl, or a single or fused ring aromatic heterocyclic group;
R_6 represents H or up to three substituents independently selected from the list consisting of: alkyl, alkenyl, aryl, alkoxy, hydroxy, halogen, nitro, cyano, carboxy, carboxamido, sulphonamido, alkoxycarbonyl, trifluoromethyl, acyloxy, amino or mono- or di-alkylamino;
R_7 is H or halo;
a is 1-6; and
any of R_2, R_5, R_9, and R_{10} may optionally be substituted one or more times by halo, hydroxy, amino, cyano, nitro, carboxy or oxo;
not being a compound wherein R_1 is H, R_2 is cycloalkyl, R_3 is methyl, R_4 is NH_2, R_5 is phenyl, and R_6 and R_7 are H.

2 A compound as claimed in any preceding claim, wherein R_4 is NR_8R_9 and R_8 and R_9 together with the N atom to which they are attached form a five- or six-membered saturated heterocyclic ring.

3 A compound as claimed in claim 2, wherein said heterocyclic ring is a six-membered ring and said ring is substituted once at the meta- or para- position thereof by R_{11}.

4 A compound as claimed in claim 1, wherein R_4 is NR_8R_9; R_8 is H and R_9 is H, alkyl, aryl, cycloalkyl or $R_{10}R_{11}$ where R_{10} is phenyl.

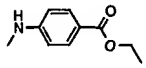
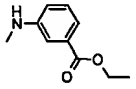
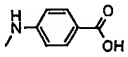
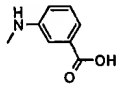
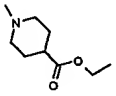
5 A compound as claimed in claim 4, wherein R_9 is $R_{10}R_{11}$ and R_{11} is meta- or para- linked to said phenyl group R_{10}.

6 A compound as claimed in any of claims 3-5, wherein R_{11} is carboxylate or carboxymethyl or carboxyethyl.

7 A compound as claimed in claim 1, wherein R_4 is R_{12}, and R_{12} is OH or OMe.

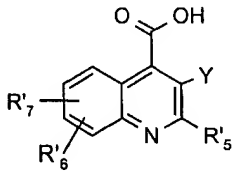
5

8 A compound as claimed in claim 1, wherein a is 1, R_6 is H, R_1 is H, R_5 is unsubstituted phenyl, R_7 is hydrogen, and R_2, R_3 and R_4 are selected from the following combinations:

R_2	R_3	R_4
Phenyl	methyl	
Cyclohexyl	methyl	
cyclohexyl	methyl	
cyclohexyl	methyl	
cyclohexyl	methyl	
cyclohexyl	methyl	
cyclohexyl	methyl	
cyclohexyl	methyl	

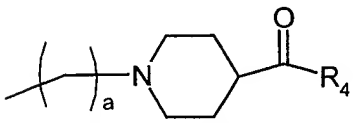
cyclohexyl	methyl	
cyclohexyl	methyl	-OH
cyclohexyl	methyl	-OMe

9 A process for the preparation of a compound of formula (I) according to any of claims 1-8, or a salt thereof and/or a solvate thereof, which process comprises reacting a compound of formula (II) or an active derivative thereof:



(II)

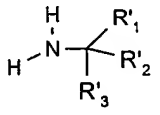
wherein R'5, R'6, and R'7 are R5, R6, and R7 respectively as defined in relation to formula (I) as claimed in claim 1 or a group convertible to R5, R6, and R7



respectively, and Y' is a group of formula (Y) or a group convertible thereto

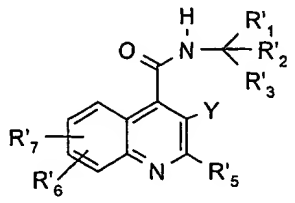
(Y)

where R4 is defined as in relation to formula (I) as claimed in claim 1, with a compound of formula (III):



(III)

wherein R'$_1$, R'$_2$ and R'$_3$ are R_1, R_2 and R_3 as defined for formula (I) as claimed in claim 1 or a group or atom convertible to R_1, R_2 and R_3 respectively; to form a compound of formula (Ib):



(Ib)

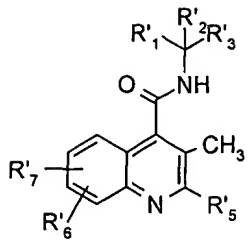
and thereafter carrying out one or more of the following optional steps:

(i) converting any one of R'$_1$, R'$_2$, R'$_3$, R'$_5$, R'$_6$, R'$_7$ and Y' to R_1, R_2, R_3, R_5, R_6, R_7 and Y respectively as required, to obtain a compound of formula (I) as claimed in claim 1;

(ii) converting a compound of formula (I) as claimed in claim 1 into another compound of formula (I) as claimed in claim 1; and

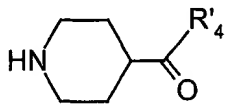
(iii) preparing a salt of the compound of formula (I) as claimed in claim 1 and/or a solvate thereof.

10 A process for the preparation of a compound of formula (I) according to any of claims 1-8, wherein a is 1, or a salt thereof and/or a solvate thereof, which process comprises reacting a compound of formula (T) or an active derivative thereof:



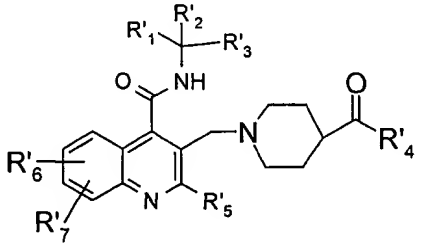
(T)

wherein each of R'1, R'2, R'3, R'5, R'6, and R'7 is R1, R2, R3, R5, R6, or R7 respectively as defined in relation to formula (I) or a group convertible to R1, R2, R3, R5, R6, or R7 respectively, providing that R2 is not an aromatic group, with a compound of formula (W)



(W)

wherein R'4 is a group R4 as defined in relation to formula (I) or a protected form thereof or a group convertible thereto, to form a compound of formula (Ib):



(Ib)

and thereafter carrying out one or more of the following optional steps:

(i) converting any one of R'1, R'2, R'3, R'4, R'5, R'6, and R'7 to R1, R2, R3, R4, R5, R6, and R7 respectively as required, to obtain a compound of formula (I);

(ii) converting a compound of formula (I) into another compound of formula (I); and

(iii) preparing a salt of the compound of formula (I) and/or a solvate thereof.

11 A pharmaceutical composition comprising a compound of formula (I) according to any of claims 1-8, or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier.

12 A compound of formula (I) as claimed in any of claims 1-8, or a pharmaceutically acceptable salt or solvate thereof, for use as an active therapeutic substance.

13 A compound of formula (I) as claimed in any of claims 1-8, or a pharmaceutically acceptable salt or solvate thereof, for the treatment or prophylaxis of the Primary and Secondary Conditions.

14 Use of a compound of formula (I) as claimed in any of claims 1-8, or a pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for the treatment of the Primary and Secondary Conditions.

15 A method for the treatment and/or prophylaxis of the Primary and Secondary Conditions in mammals, particularly humans, which comprises administering to the mammal in need of such treatment and/or prophylaxis an effective, non-toxic pharmaceutically acceptable amount of a compound of formula (I) as claimed in any of claims 1-8 or a pharmaceutically acceptable salt or solvate thereof.

R_5 is branched or linear alkyl, cycloalkyl, cycloalkylalkyl, aryl, or a single or fused ring aromatic heterocyclic group;

R_6 represents H or up to three substituents independently selected from the list consisting of: alkyl, alkenyl, aryl, alkoxy, hydroxy, halogen, nitro, cyano, carboxy, carboxamido, sulphonamido, alkoxycarbonyl, trifluoromethyl, acyloxy, amino or mono- or di-alkylamino;

R_7 is H or halo;

a is 1-6; and

any of R_2, R_5, R_9, and R_{10} may optionally be substituted one or more times by halo, hydroxy, amino, cyano, nitro, carboxy or oxo;

a process for preparing such compounds, a pharmaceutical composition comprising such compounds and the use of such compounds and composition in medicine.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 01/14140

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/47 A61K31/4709 A61P11/06 C07D401/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 00 31037 A (NADLER GUY MARGUERITE MARIE G ;MORVAN MARCEL (FR); SMITHKLINE BEEC) 2 June 2000 (2000-06-02) cited in the application claim 13; example 36	1-13

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 February 2002	08/03/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	De Jong, B

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Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 01/14140

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 15 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compounds.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all *required additional search fees* were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 01/14140

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0031037 A	02-06-2000	AU 1777000 A	13-06-2000
		BR 9915475 A	18-12-2001
		WO 0031037 A1	02-06-2000
		EP 1131295 A1	12-09-2001
		NO 20012473 A	18-07-2001